TYROSINASE INHIBITOR AND USE THEREOF

The present invention claims priority to seven prior patent applications filed with the China National Intellectual Property Administration, all entitled “Tyrosinase Inhibitor and Use Thereof”, with the respective application numbers and filing dates as follows: Patent Application No. 202410353481.8 filed on March 26, 2024; Patent Application No. 202410533155.5 filed on April 29, 2024; Patent Application No. 202410711104.7 filed on June 3, 2024; Patent Application No. 202410909706.3 filed on July 8, 2024; Patent Application No. 202411025194.0 filed on July 29, 2024; Patent Application No. 202411775451.2 filed on December 4, 2024; and Patent Application No. 202510322654.4 filed on March 18, 2025, and these prior applications are incorporated herein by reference in their entirety.

TECHNICAL FIELD

The present invention belongs to the field of chemical compounds, and specifically relates to a tyrosinase inhibitor compound, a composition, a preparation method and a use.

BACKGROUND

The number of melanocytes in human skin is generally consistent and unrelated to skin tone. Skin color is primarily determined by the quantity and type of melanin (black eumelanin or yellow to reddish-brown pheomelanin). Compared with individuals with dark skin, Asians and fair-skinned people have lower eumelanin levels and weaker natural protection against sunlight. Melanin also differs in its distribution across the skin. In fair-skinned individuals, most pigments reside in the basal layer, while in dark-skinned individuals, melanin diffuses throughout the stratum corneum. Multiple factors can trigger skin hyperpigmentation, including ultraviolet radiation (e.g., sunspots, freckles), genetic predisposition, abnormal pigmentation during wound healing (post-inflammatory hyperpigmentation), and abnormal pigmentation associated with skin aging (e.g., age spots). Post-inflammatory hyperpigmentation is a common problem among colored people. For example, colored men may experience pseudofolliculitis of the beard area, accompanied by abnormal pigmentation; and melasma (particularly seen on the face and neck of Asian women).

Tyrosinase is a key enzyme in the production of melanin. It mainly catalyzes three reactions: 1) hydroxylation of tyrosine to 3,4-dihydroxyphenylalanine (DOPA); 2) oxidation of DOPA to DOPAquinone; and 3) oxidation of DHI (5,6-dihydroxyindole) to indolequinone. Tyrosinase is a member of the copper protein family, possessing two copper ions at its active site. The binuclear copper ions have three major redox states: 1) the reduced Cu^{+}- Cu^{+}- state; 2) the Cu^{2+}-O_2- Cu^{2+} state that reversibly binds to O_2 to form peroxide; 3) the state where Cu ions are bridged by small ligands such as H_2O. The Cu^{2+}-O_2-Cu^{2+} redox state is critical to tyrosinase activity. The reaction catalyzed by tyrosinase to attach a second hydroxyl group to the ortho position of monophenols (e.g., tyrosine) serves as a core step in melanin biosynthesis. There are two primary approaches to

inhibit melanin production: direct interaction with tyrosinase, or chelation of the copper catalytic center to indirectly suppress tyrosinase activity.

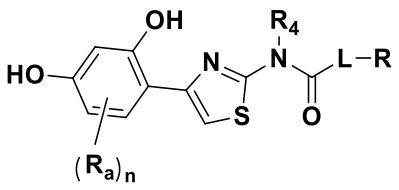
Currently, substances commonly used for skin whitening include hydroquinone, hexadecane-1,16-dioic acid, kojic acid and its derivatives, arbutin, ascorbic acid and its derivatives, flavonoids, ellagic acid and its derivatives, tranexamic acid and various resorcinol derivatives, 4-n-butylresorcinol, 4-n-hexylresorcinol and 4-(1-phenylethyl)benzene-1,3-diol. Hydroquinone was one of the earliest skin bleaching agents. For example, Albert Kligman et al. developed the so-called "Triformula," which is a combination of 0.1% retinoic acid, 5.0% hydroquinone, and 0.1% dexamethasone. However, long-term use of hydroquinone can lead to irreversible changes in the skin pigment system, produce cytotoxicity to melanocytes, and pose a risk of permanent skin depigmentation. In China, the addition of hydroquinone to skin care products is restricted, and it is only available for use via prescription.

Research conducted by Beiersdorf reveals that hydroquinone, arbutin, kojic acid, 4-n-butylresorcinol, 4-n-hexylresorcinol and 4-(1-phenylethyl)benzene-1,3-diol exhibit weak or even no inhibitory activity against human tyrosinase. The company has reported a series of resorcinol thiazole compounds which deliver relatively potent inhibitory effects on human tyrosinase.

The resorcinol derivatives disclosed in the prior art suffer from insufficient inhibitory activity against human tyrosinase and poor physicochemical stability, failing to meet the needs of patients with pigmentation disorders. There is an urgent demand to develop compounds that exert potent reversible inhibition on human tyrosinase and possess favorable physicochemical properties. Such compounds are expected to be effective at extremely low concentrations while posing no toxicity to melanocytes or the skin.

SUMMARY OF THE INVENTION

To address the above technical problems, the present invention provides a compound represented by formula (I), as well as racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof, or prodrug compounds thereof:



(I)

wherein the R_a groups are the same or different, and are each independently selected from H, OH, CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy or halo-C_{1-6} alkoxy;

L is absent, or is selected from C_{1-3} alkylene which is unsubstituted or optionally substituted with one, two or more L_a groups; the L_a groups are the same or different and are each independently selected from H or C_{1-6} alkyl;

R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: C_{1-12} alkyl, C_{3-12} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, $-NR_1R_2$ or $-OR_3$; wherein R_1, R_2 and R_3 are the same or different, and are each independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl;

the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, $-S(=O)_2C_{1-6}$ alkyl, 3- to 8-membered heterocyclyl, $-C_{1-6}$ alkylene-O-C_{1-6} alkyl, $-C(=O)-R_5$, $-C(=O)OR_6$, $-C(=O)NR_7R_8$ or 5- to 14-membered heteroaryl; wherein R_5, R_6, R_7 and R_8 are the same or different, and are each independently selected from H or C_{1-6} alkyl;

alternatively, two R_b groups linked to different carbon atoms, together with the carbon atoms to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b1} groups: C_{3-8} carbocyclic rings or 3- to 8-membered heterocyclic rings;

alternatively, two R_b groups linked to the same carbon atom, together with the carbon atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: C_{3-8} carbocyclic rings or 3- to 8-membered heterocyclic rings;

the R_{b1} groups and R_{b2} groups are the same or different, and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-6} alkyl, C_{1-6} alkoxy, $-C_{1-6}$ alkylene-O-C_{1-6} alkyl or NH_2;

the R_{bb} groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), C_{1-6} alkyl, C_{1-6} alkoxy or NH_2;

R_4 is selected from H; alternatively, R_4 is linked to an atom on the R group to jointly form a heterocycle containing a lactam structure, the heterocycle is a 5- to 8-membered heterocycle which is unsubstituted or optionally substituted with one, two or more R_{4a} groups; the R_{4a} groups are the same or different and are each independently selected from OH, CN, halogen, oxo (=O), C_{1-6} alkyl, halo-C_{1-6} alkyl or C_{1-6} alkoxy;

n is selected from 0, 1, 2 or 3.

According to some embodiments, the R_a groups are the same or different and are each independently selected from OH, CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy or halo-C_{1-6} alkoxy, and n is selected from 1, 2 or 3.

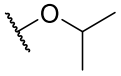
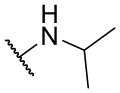
According to some embodiments, the R_a groups are the same or different and are each independently selected from OH, CN, F, Cl, Br, methyl, trifluoromethyl or methoxy.

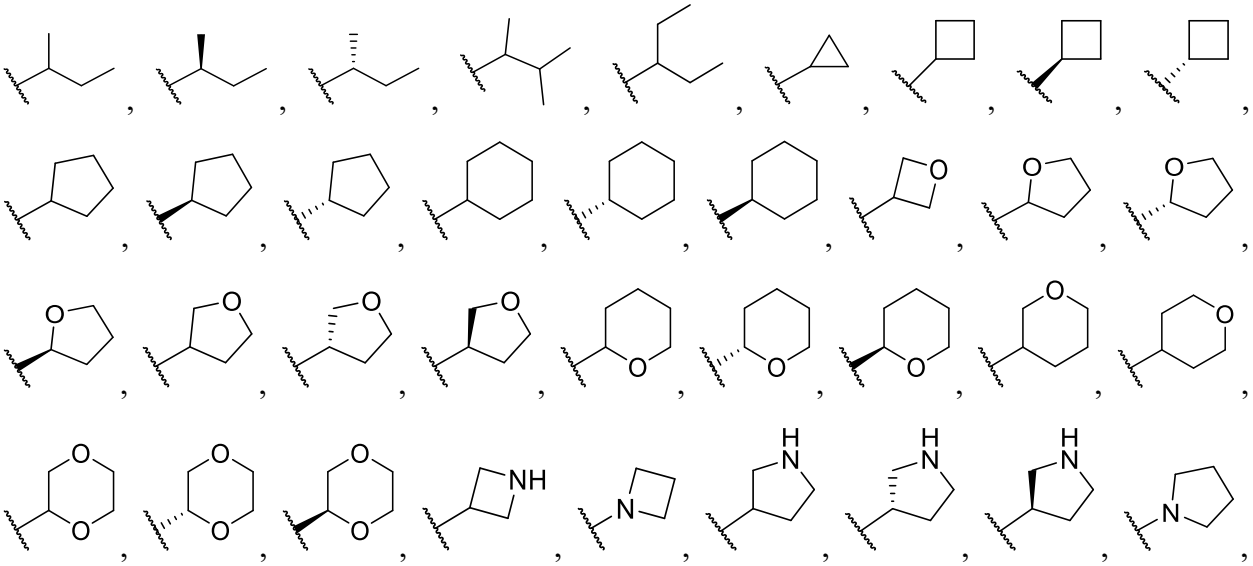
According to some embodiments, n is selected from 1.

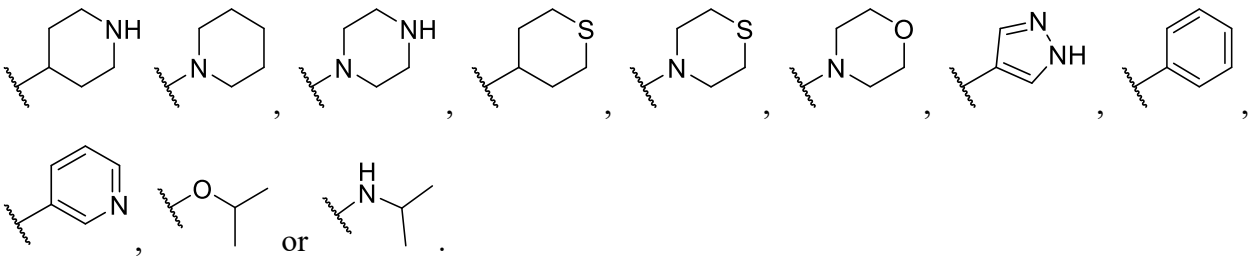
According to some embodiments, L is absent.

According to some embodiments, L is selected from-CH_2-, -CH_2CH_2- or -$CH(CH_3)$-.

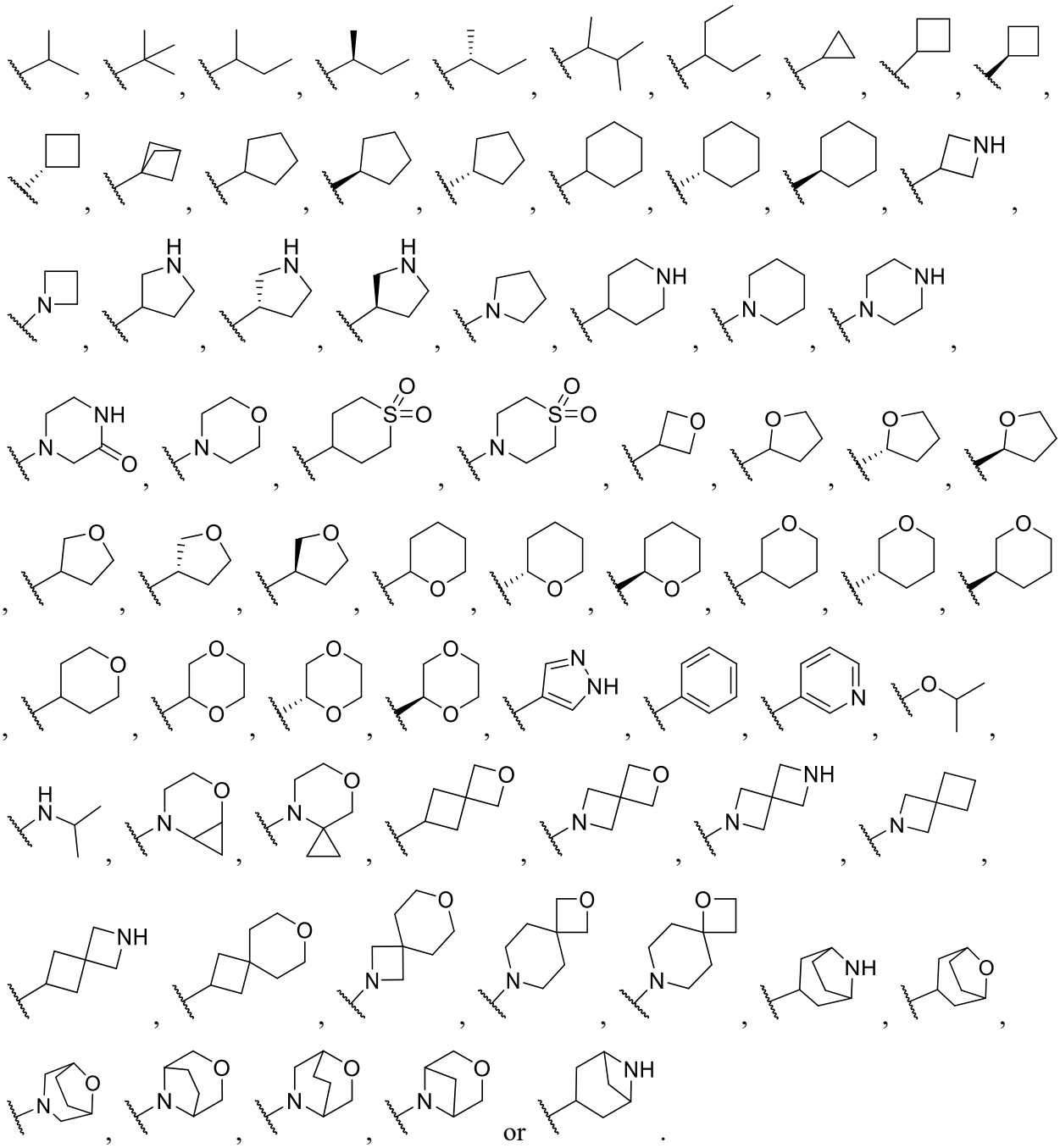
According to some embodiments, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, -NR_1R_2 or -OR_3.

According to some embodiments, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, 3-methylbutan-2-yl, pentan-3-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuryl, tetrahydro-2*H*-pyranyl, 1,4-dioxanyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydro-2*H*-thiopyranyl, thiomorpholinyl, phenyl, pyridyl, pyrazolyl,  or .

According to some embodiments, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: , , 



According to some embodiments, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups:

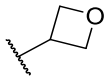
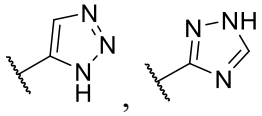


According to some embodiments, the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-3} alkyl, C_{1-3} alkoxy,

NH_2, -S(=O)$_2$C$_{1-3}$ alkyl, 3- to 8-membered heterocyclyl, -C$_{1-3}$ alkylene-O-C$_{1-3}$ alkyl, -C(=O)-R_5, -C(=O)OR_6, -C(=O)NR_7R_8 or 5- to 6-membered heteroaryl.

According to some embodiments, R_5, R_6, R_7 and R_8 are the same or different, and are each independently selected from H or methyl.

According to some embodiments, the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, C$_{1-6}$ alkyl, halo-C$_{1-6}$ alkyl, C$_{1-6}$ alkoxy, hydroxy-C$_{1-6}$ alkyl (HO-C$_{1-6}$ alkyl), -C(=O)-C$_{1-6}$ alkyl, -S(=O)$_2$C$_{1-6}$ alkyl, 3- to 6-membered heterocyclyl, -C$_{1-6}$ alkyl-O-C$_{1-6}$ alkyl, -C(=O)OH, -C(=O)OC$_{1-6}$ alkyl, -C(=O)NH_2, -C(=O)N(C$_{1-6}$ alkyl)$_2$, -C$_{1-6}$ alkylene-O-halo-C$_{1-6}$ alkyl, 5- to 6-membered heteroaryl.

According to some embodiments, the R_b groups are the same or different and are each independently selected from H, OH, CN, F, Cl, Br, methyl, ethyl, methoxy, hydroxymethyl, hydroxyethyl (e.g., 1-hydroxyethyl, 2-hydroxyethyl), oxo (=O), difluoromethyl, acetyl, methanesulfonyl, oxetanyl (e.g., ), methoxyethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, -C(=O)OH, -C(=O)OCH_3, -C(=O)NH_2, -C(=O)N$(CH_3)_2$, -$CH_2CH_2OCH_2CF_3$, -$CH_2CH_2OCH_2CHF_2$, triazolyl (e.g., ), tetrazolyl or isoxazol-3(2*H*)-keto.

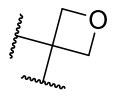
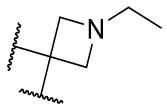
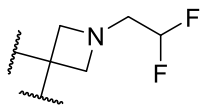
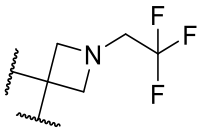
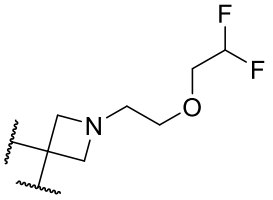
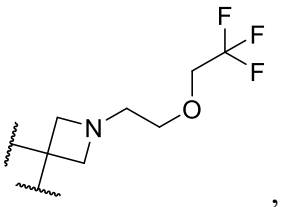
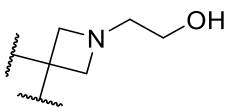
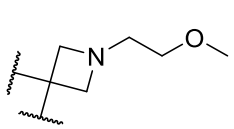
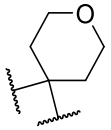
According to some embodiments, the R_b groups linked to two adjacent carbon atoms, together with the atoms to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b1} groups: C$_{3-8}$ cycloalkyl, C$_{3-8}$ cycloalkenyl or a 3- to 8-membered heterocycle.

According to some embodiments, the R_b groups linked to two adjacent carbon atoms, together with the atoms to which they are linked, jointly form a cyclopropane ring.

According to some embodiments, two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: C$_{3-8}$ cycloalkyl, C$_{3-8}$ cycloalkenyl or a 3- to 8-membered heterocycle.

According to some embodiments, two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: a cyclopropane ring, a cyclobutane ring, an oxetane ring, an azetidine ring or a tetrahydro-2*H*-pyran ring.

According to some embodiments, two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form a cyclopropane ring, a cyclobutane ring, an oxetane

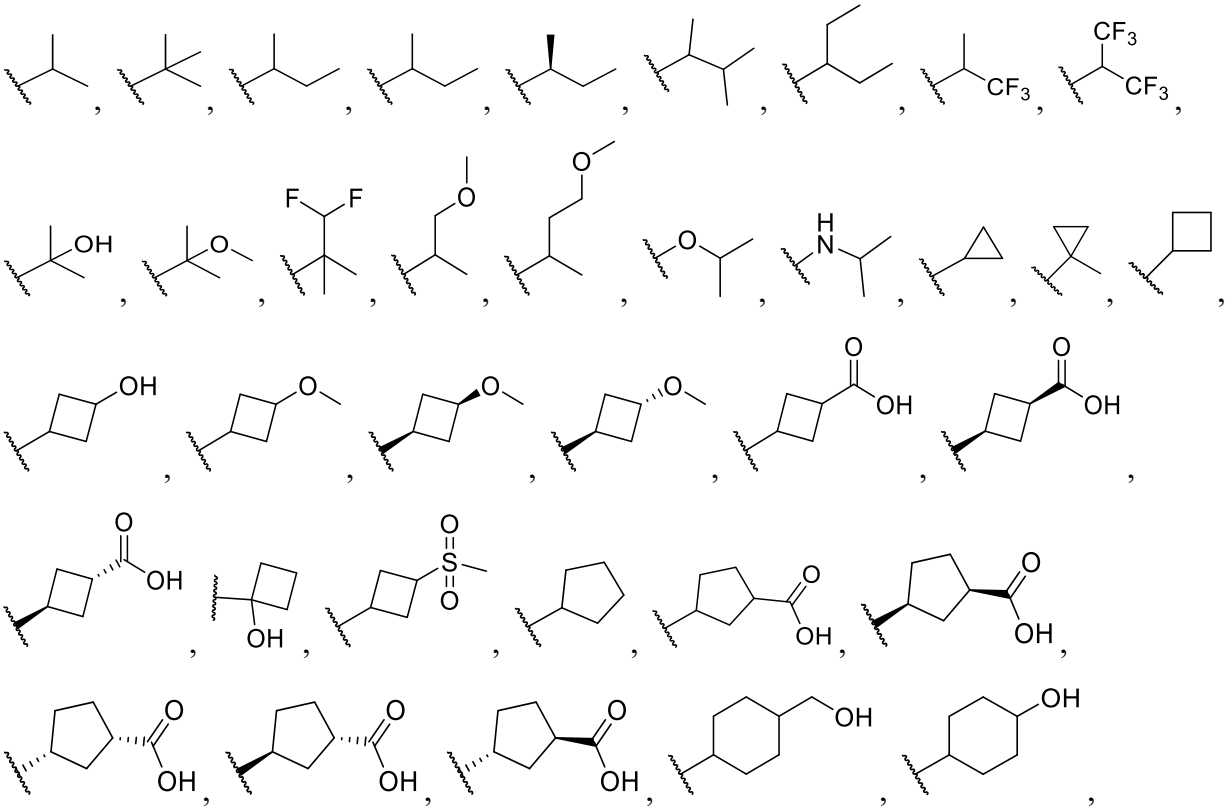
ring (e.g., ), , , , , , ,  or .

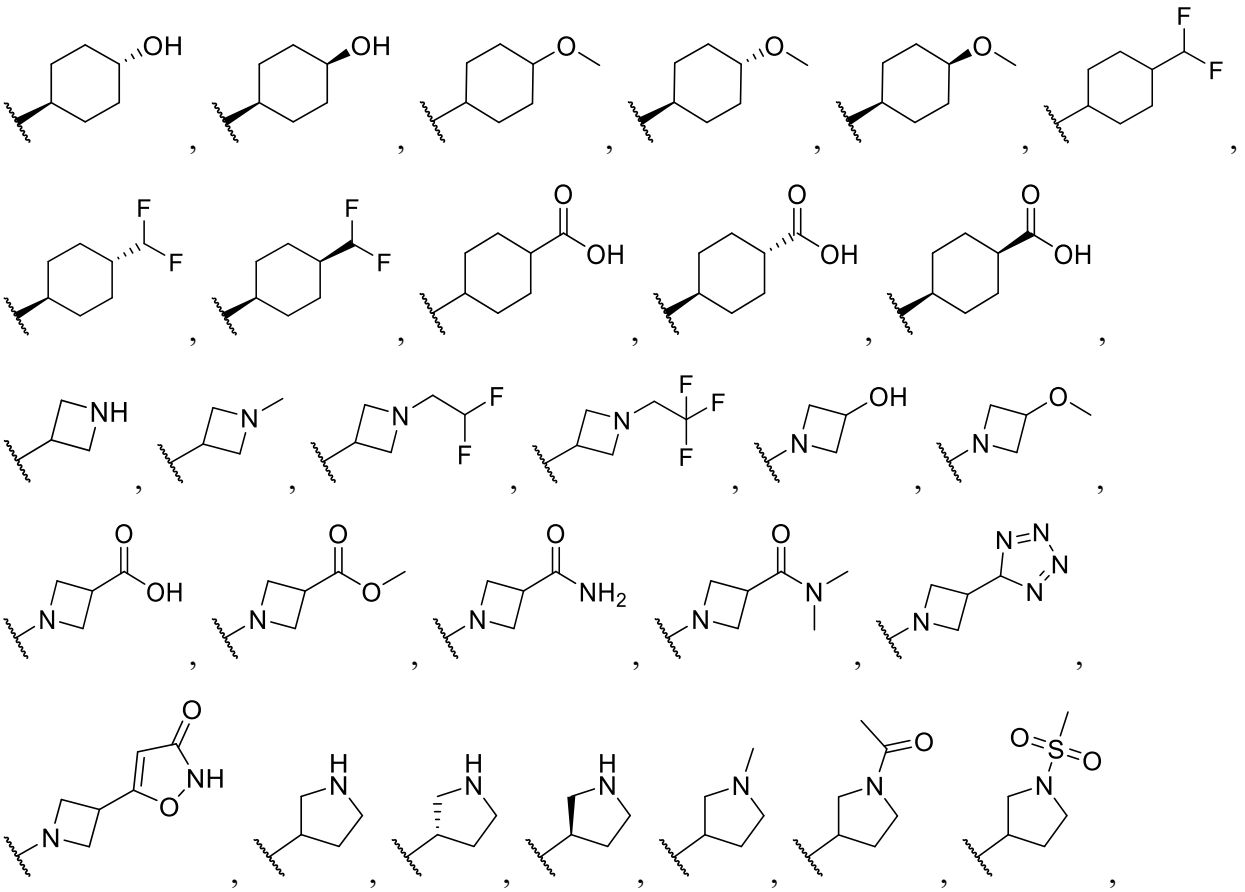
According to some embodiments, the R_b groups linked to two non-adjacent carbon atoms are linked via their terminal groups to jointly form C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$).

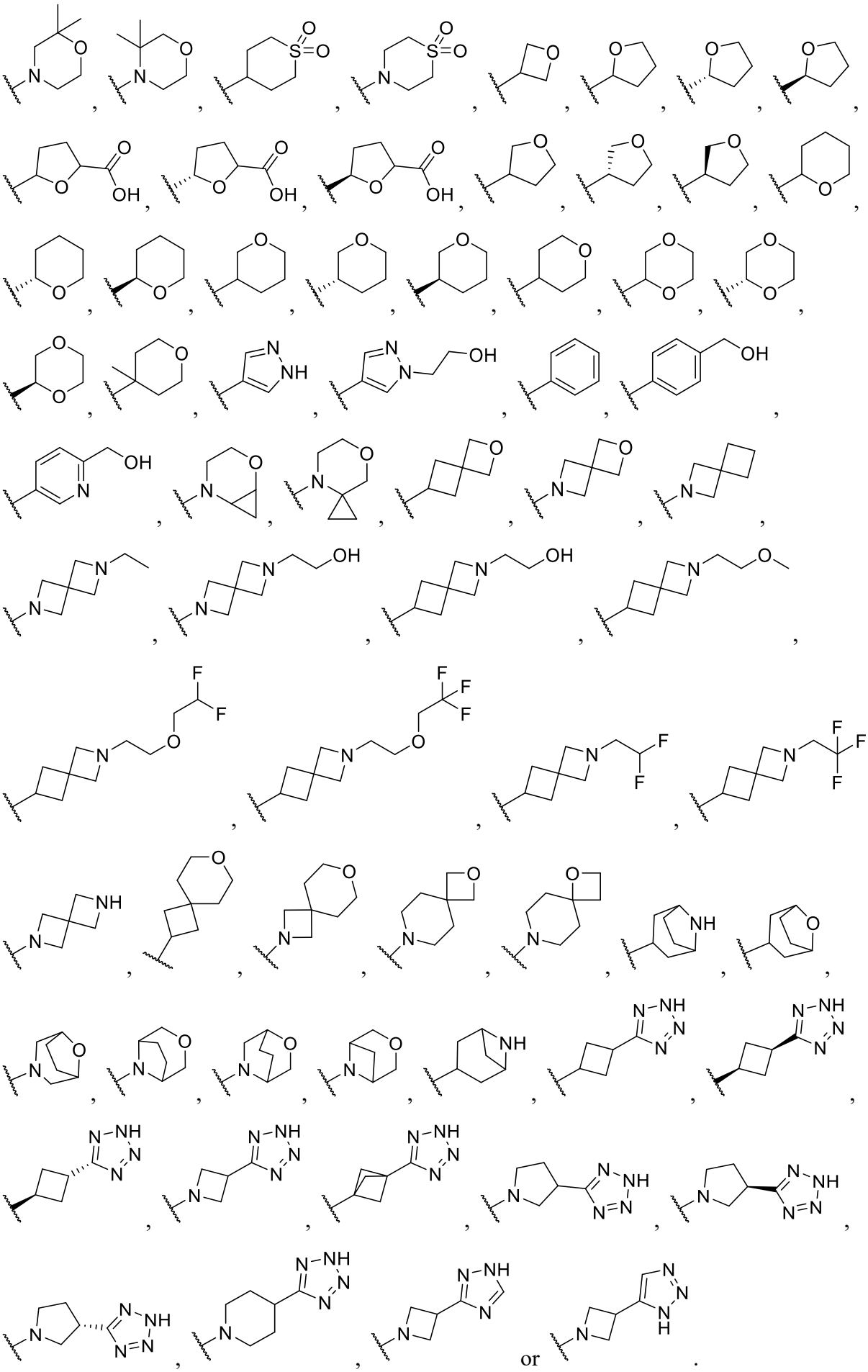
According to some embodiments, the R_{b1} groups and R_{b2} groups are the same or different, and are each independently selected from OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-3} alkyl, C_{1-3} alkoxy or NH_2; the R_{bb} groups are the same or different, and are each independently selected from H, OH, CN, C_{1-6} alkoxy (e.g., methoxy) or halogen (e.g., F, Cl, Br).

According to some embodiments, the R_{b2} groups are the same or different and are each independently selected from methyl, ethyl, hydroxyethyl (e.g., 1-hydroxyethyl, 2-hydroxyethyl) or methoxyethyl.

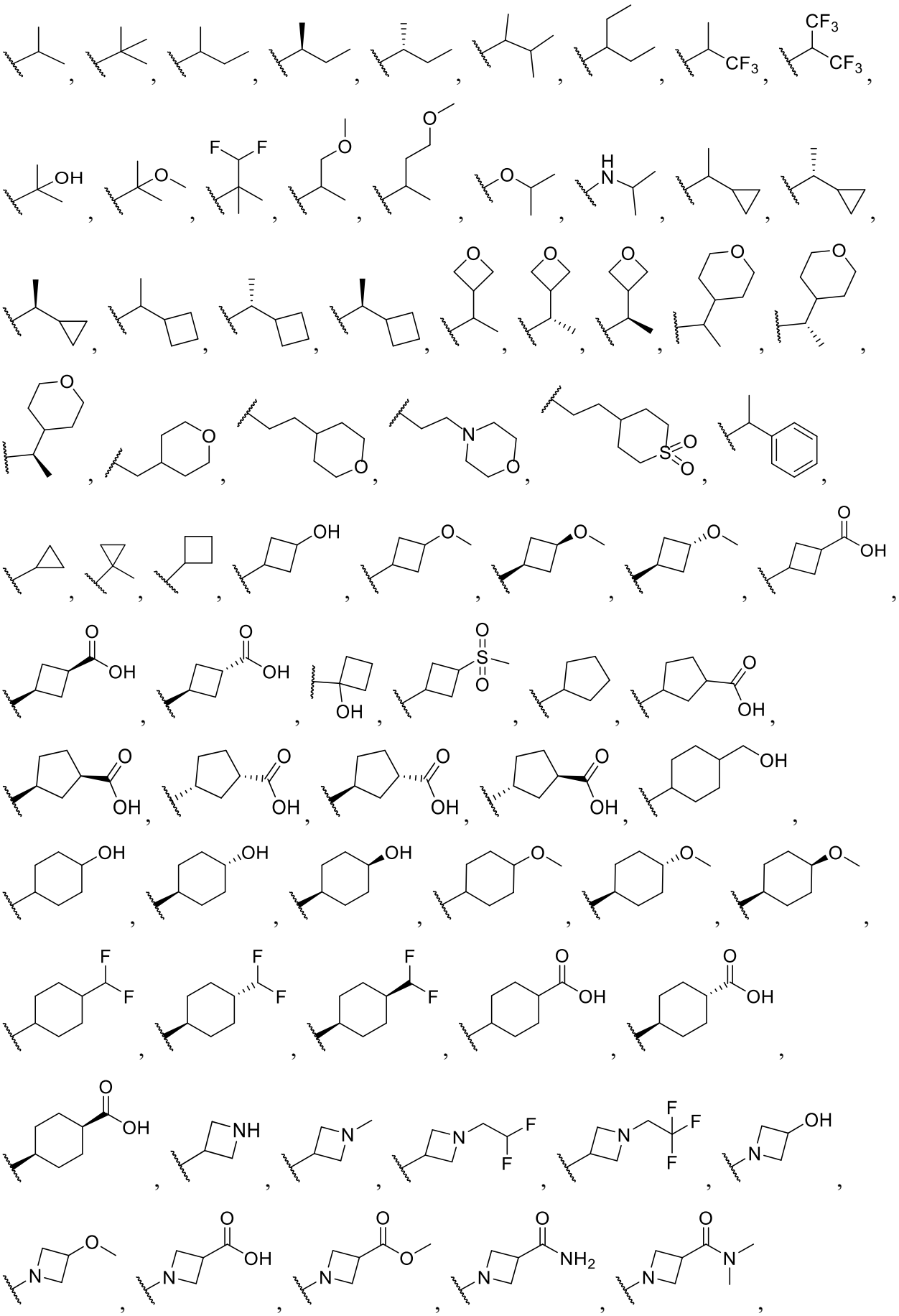
According to some embodiments, R is selected from the following groups:

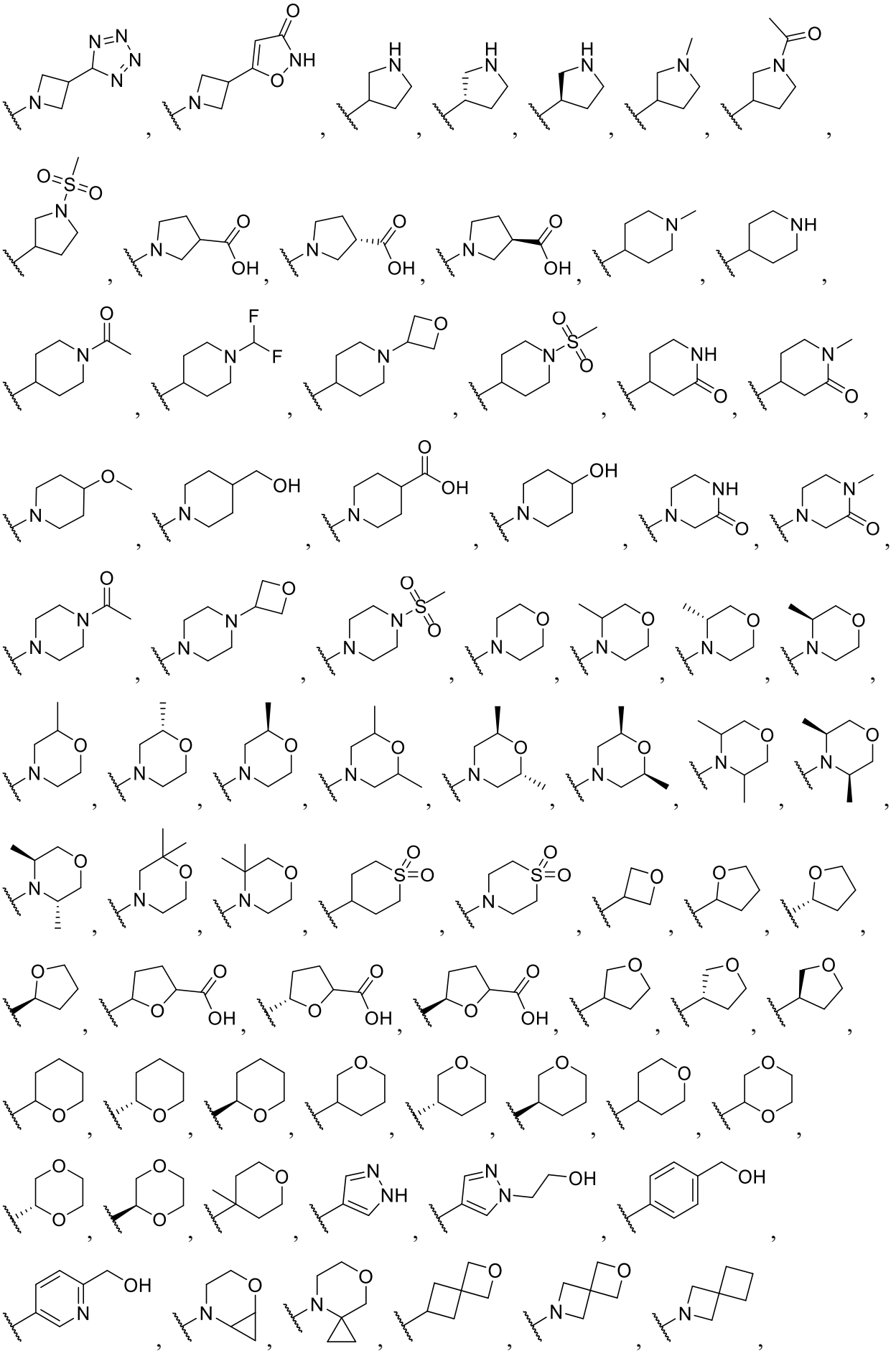


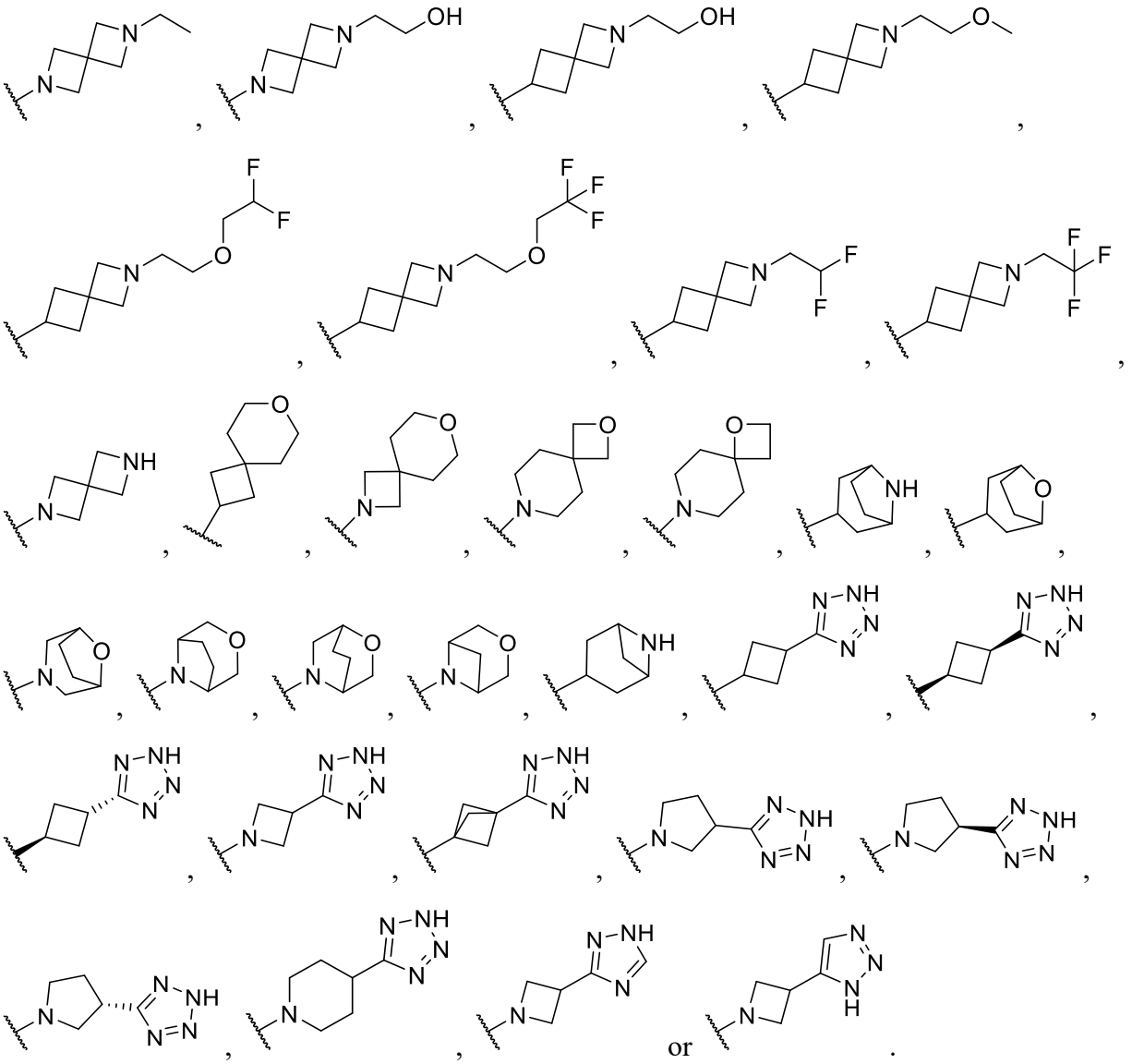




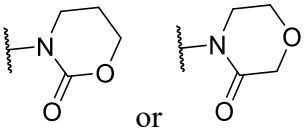
According to some embodiments, -L-R is selected from the following groups:



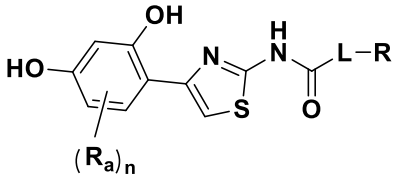




According to some embodiments, R_4 is linked to an atom on the R group to jointly form



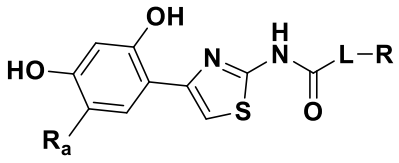
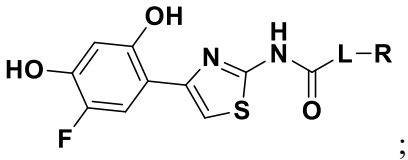
According to some embodiments, the compound represented by formula (I) is selected from the following structures:



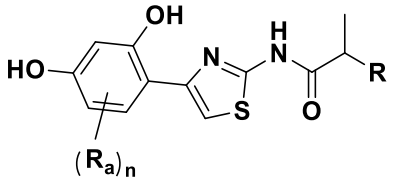
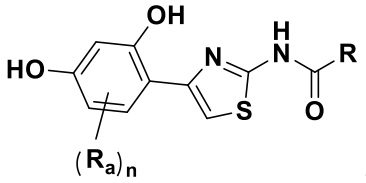
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wherein R_a, L, R and n are as defined herein.

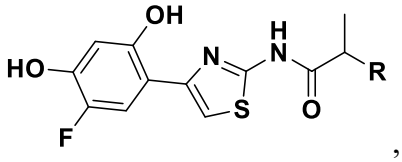
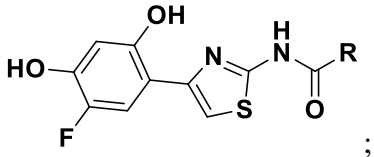
According to some embodiments, the compound represented by formula (I) is selected from the following structures:

(IA-1) (IA-2)

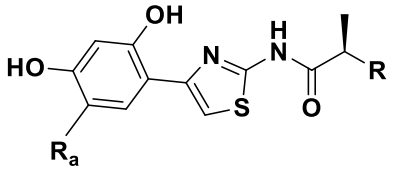
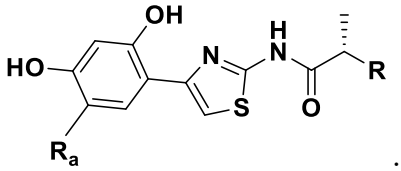
(IA-3) (IA-4)

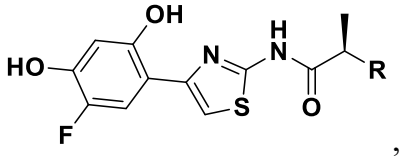
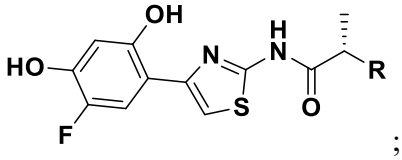
(IA-5) (IA-6)

wherein R_a, L, R and n are as defined herein.

According to some embodiments, the compound represented by formula (I) is selected from the following structures:

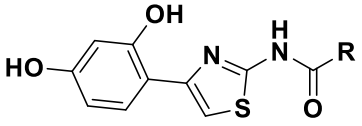
(IB-1) (IB-2)

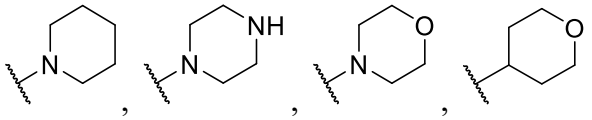
(IB-3) (IB-4)

wherein R_a and R are as defined herein.

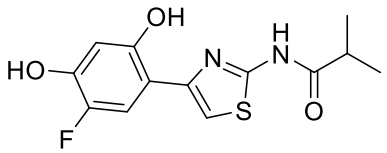
According to some embodiments, the compound represented by formula (I) is selected from the following structures:



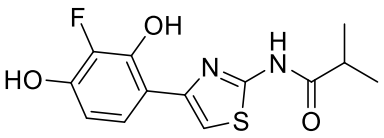
(I-2)

wherein R is as defined herein, provided that R cannot be the following groups: unsubstituted C_{3-8} cycloalkyl, .

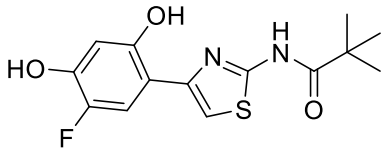
According to some embodiments, the compound represented by formula (I) is selected from the following structures:



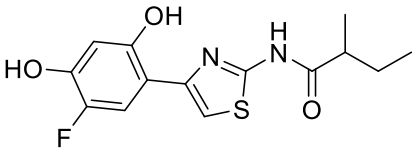
Cpd-01 ,



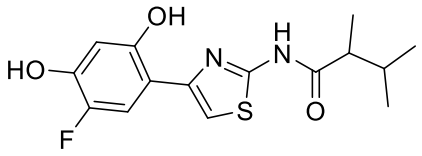
Cpd-02 ,



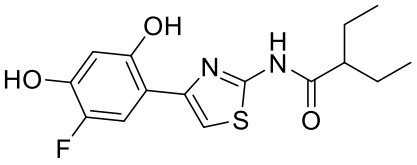
Cpd-03 ,



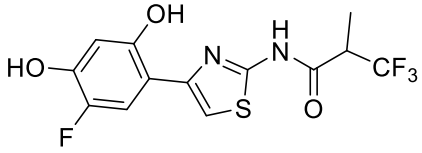
Cpd-04 ,



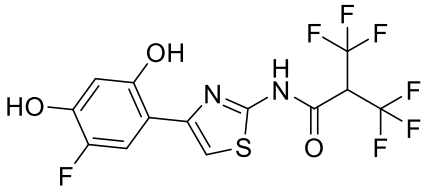
Cpd-05 ,



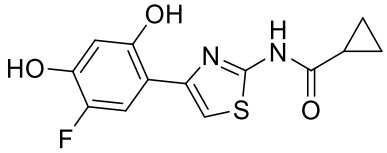
Cpd-06 ,



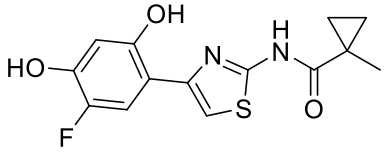
Cpd-07 ,



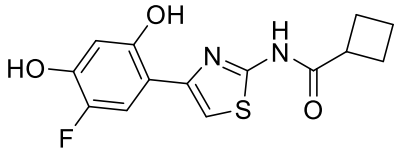
Cpd-08 ,



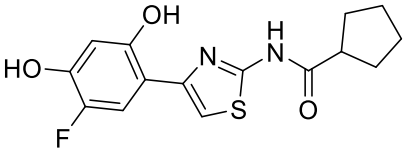
Cpd-09 ,



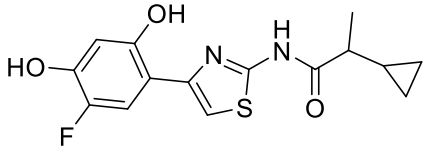
Cpd-10 ,



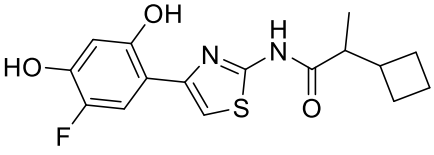
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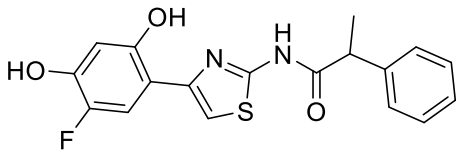
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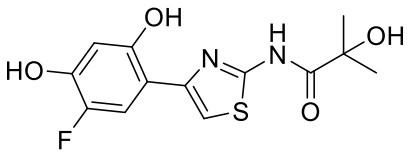
Cpd-13 ,



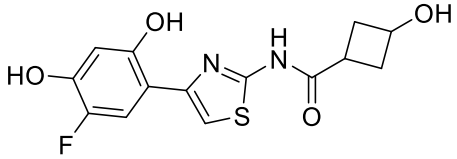
Cpd-14 ,



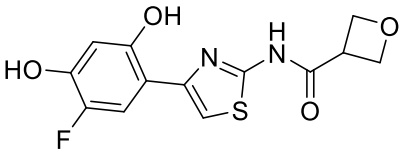
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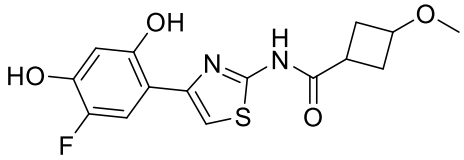
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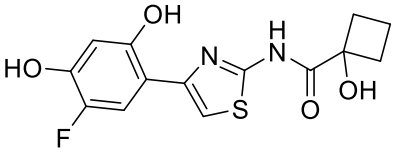
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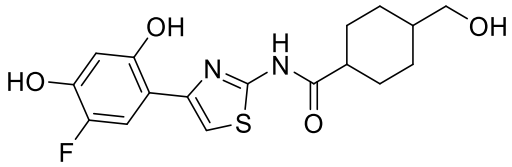
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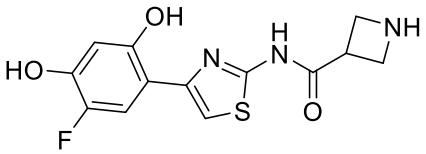
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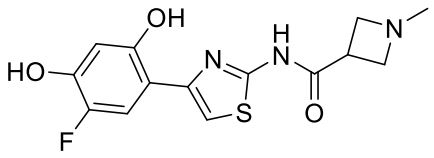
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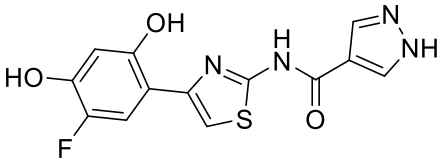
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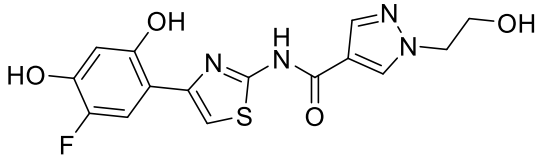
Cpd-22 ,



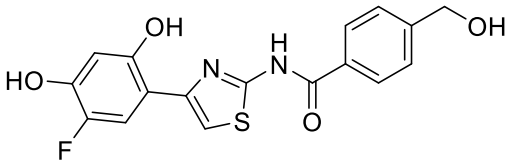
Cpd-23 ,



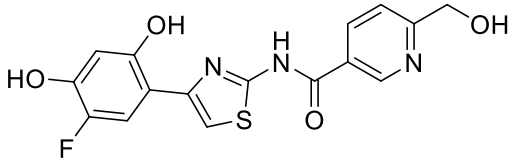
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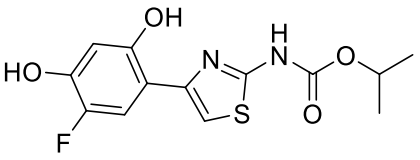
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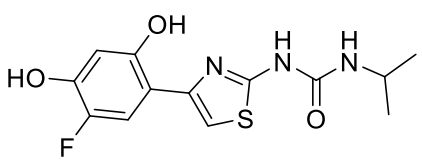
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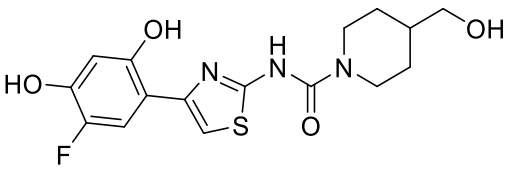
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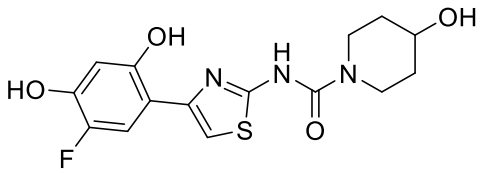
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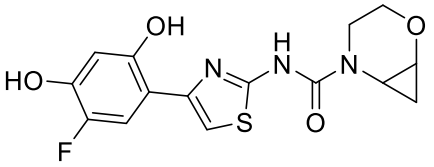
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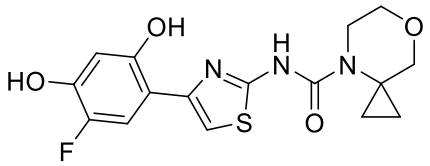
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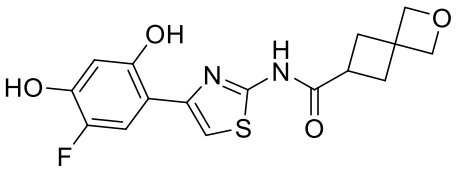
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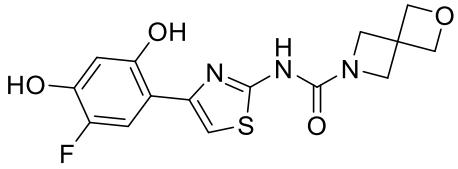
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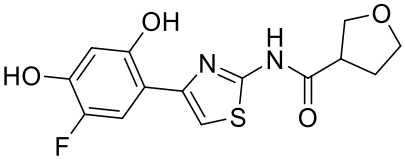
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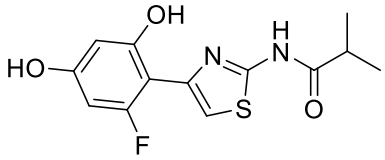
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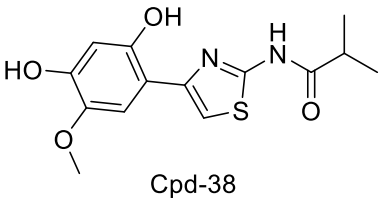
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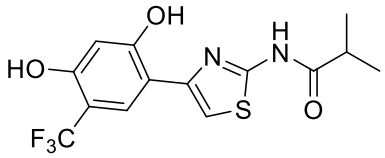
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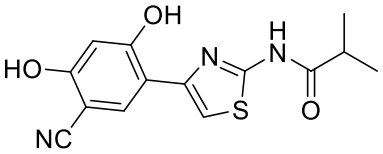
Cpd-37 ,



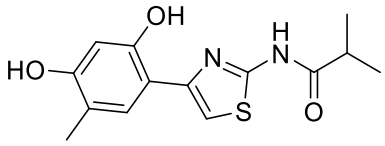
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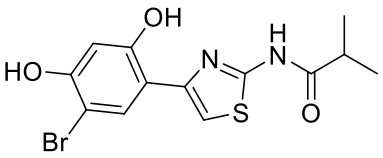
Cpd-39 ,



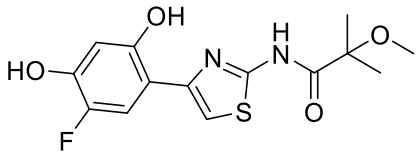
Cpd-40 ,



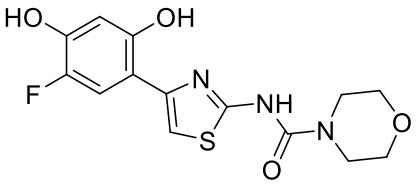
Cpd-41 ,



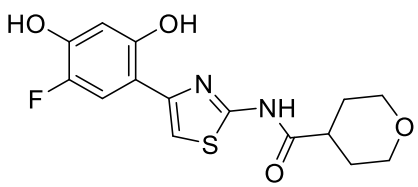
Cpd-42 ,



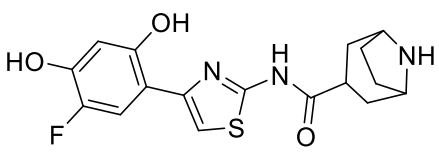
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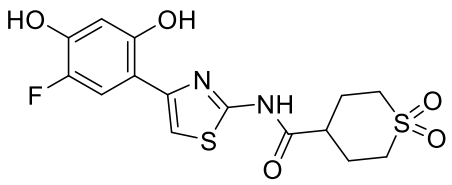
Cpd-44 ,



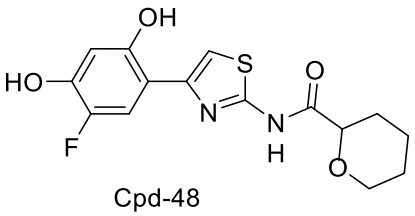
Cpd-45 ,



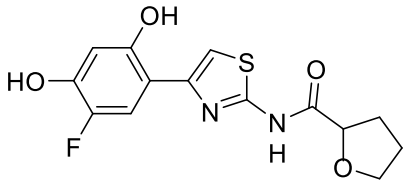
Cpd-46 ,



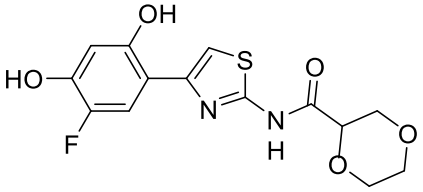
Cpd-47 ,



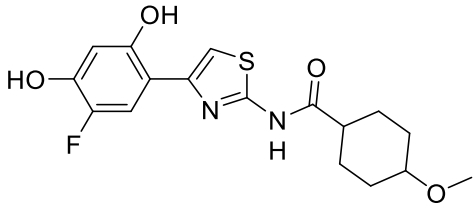
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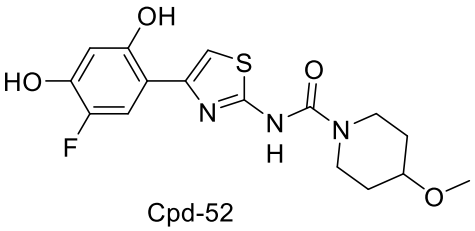
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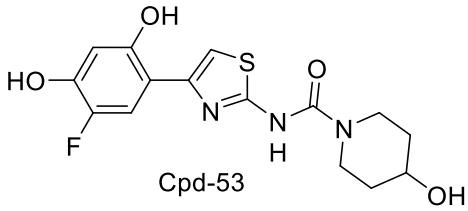
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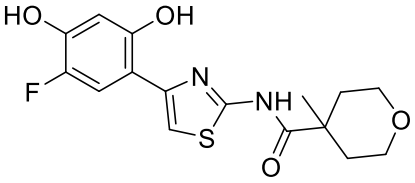
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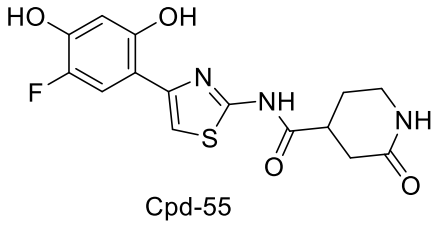
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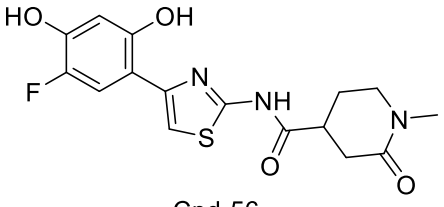
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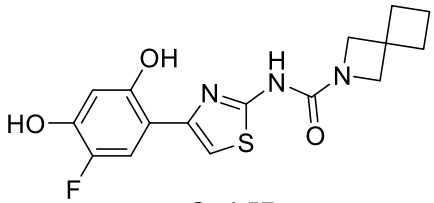
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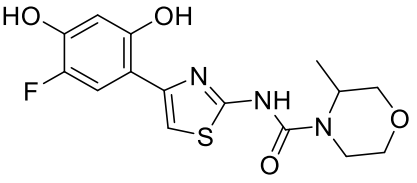
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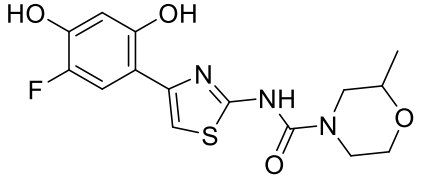
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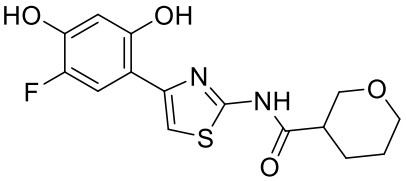
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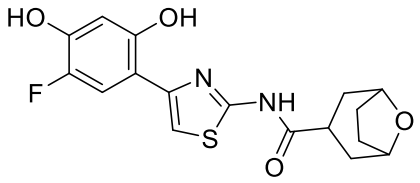
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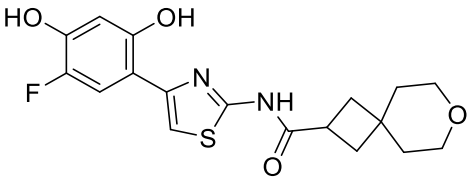
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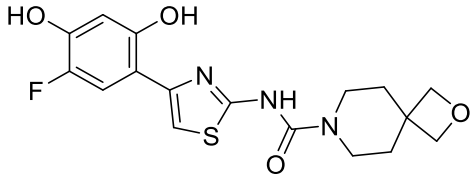
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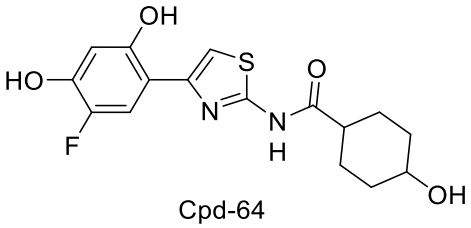
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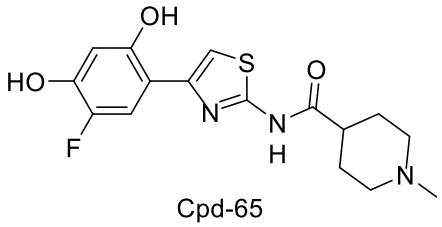
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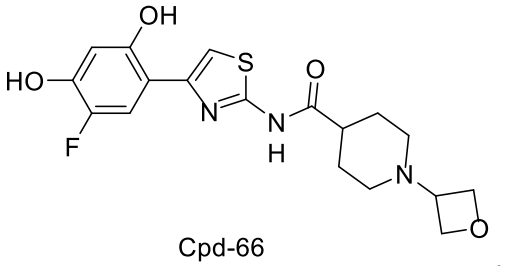
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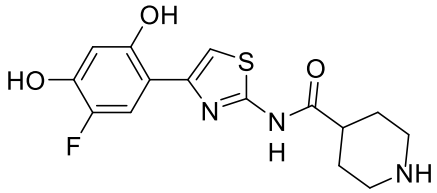
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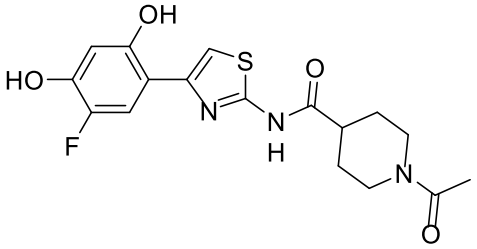
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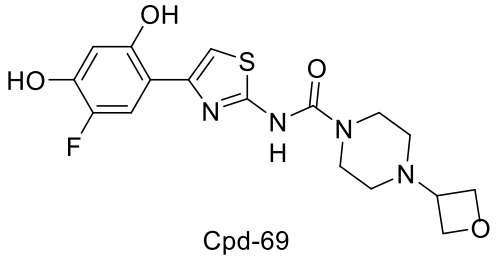
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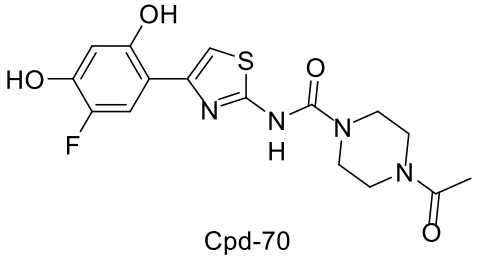
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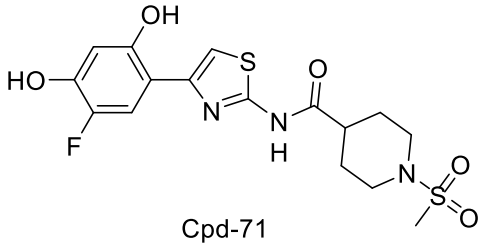
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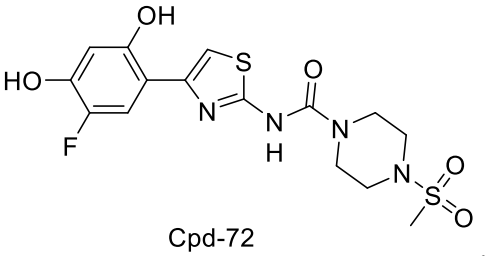
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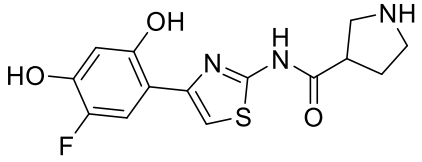
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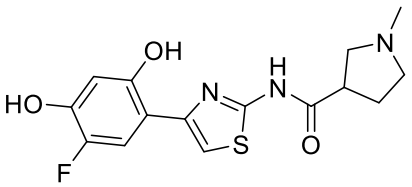
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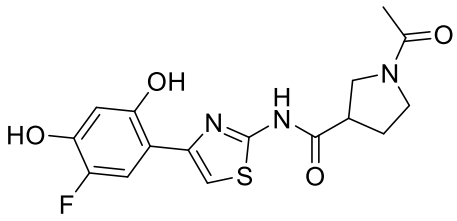
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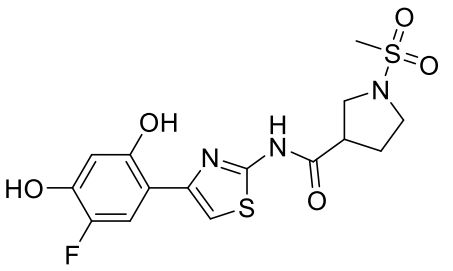


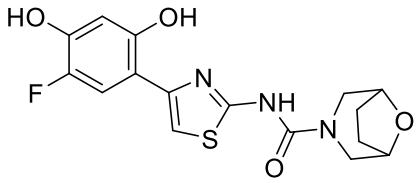
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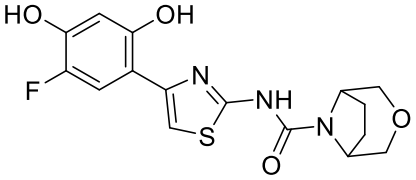


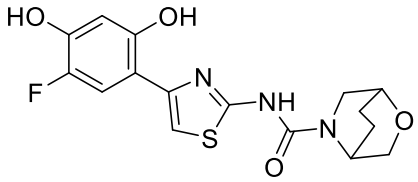
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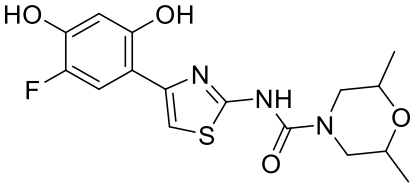


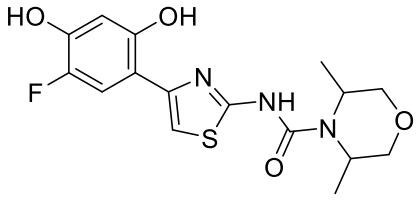
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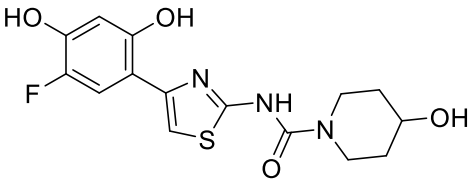


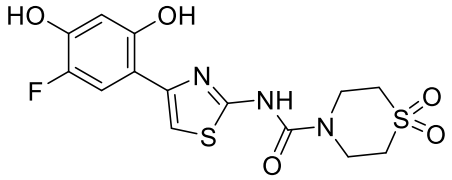
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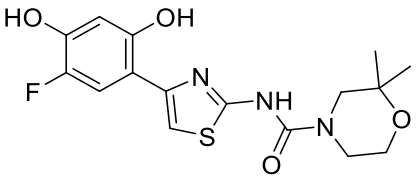


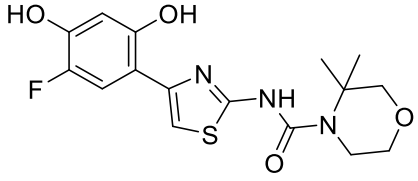
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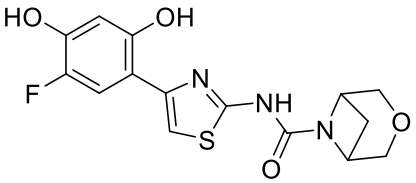


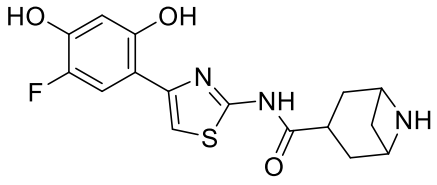
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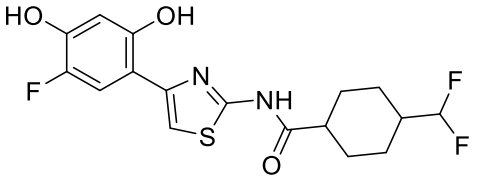


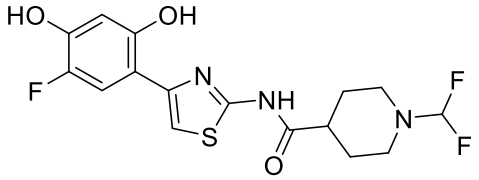
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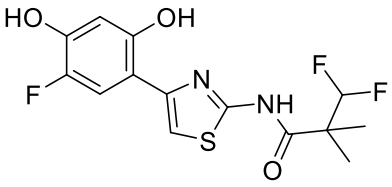
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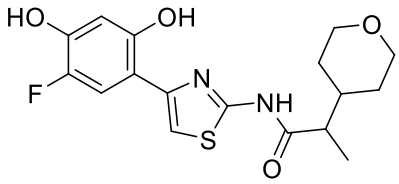
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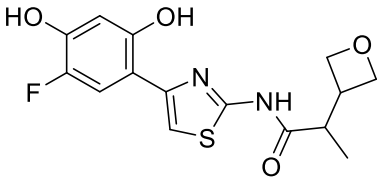
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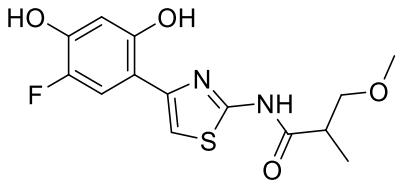
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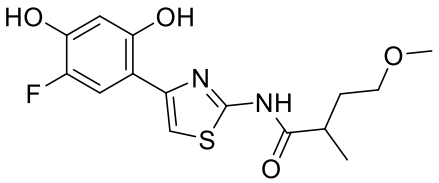
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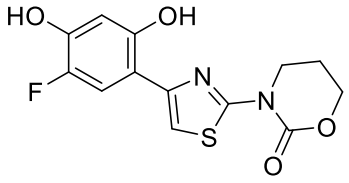
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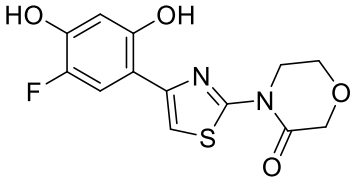
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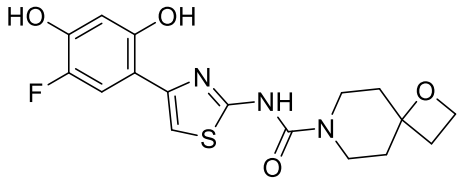
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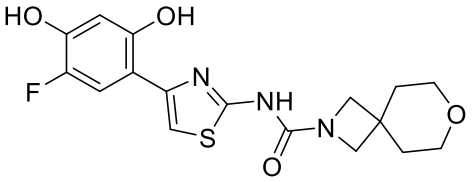
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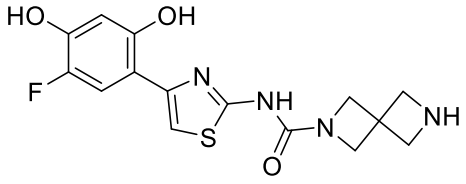
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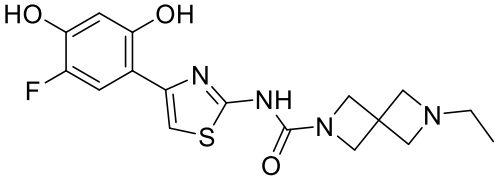
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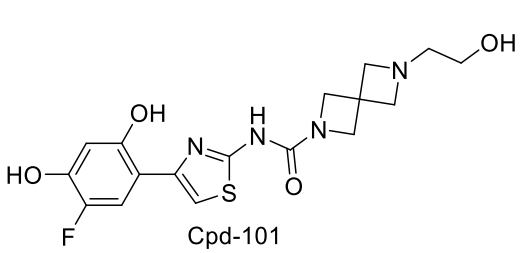
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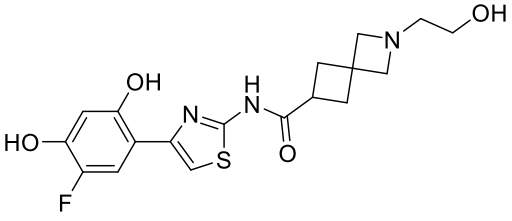
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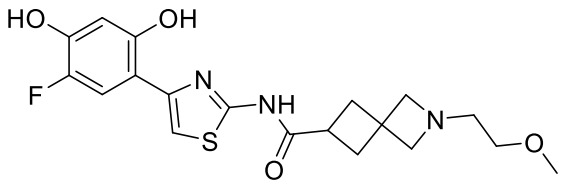
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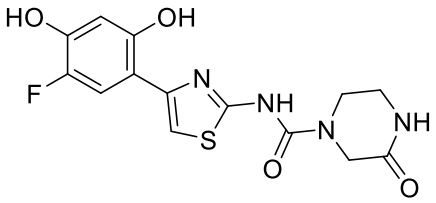
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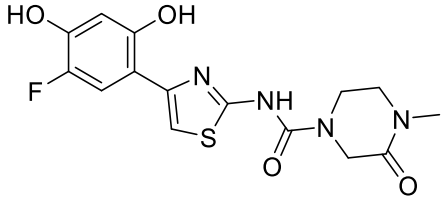
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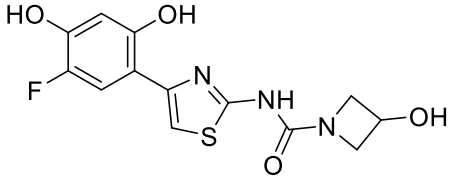
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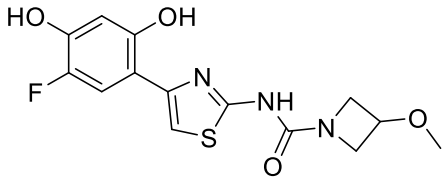
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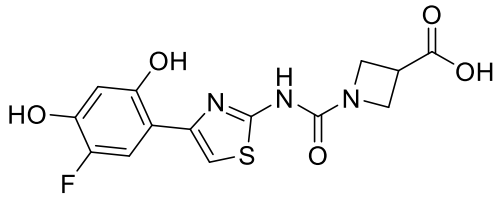
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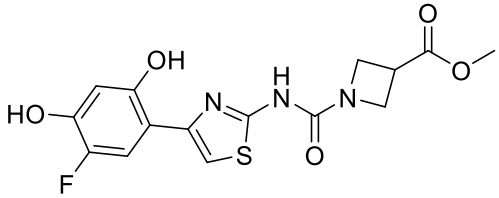
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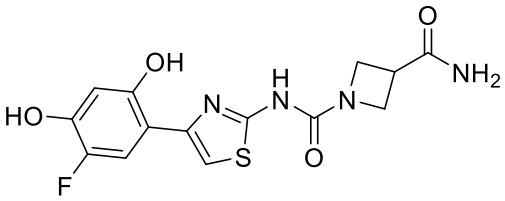
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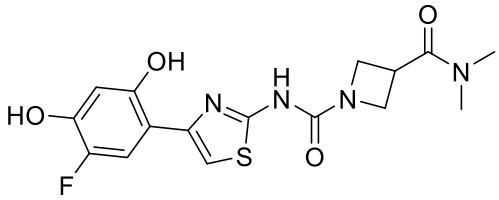
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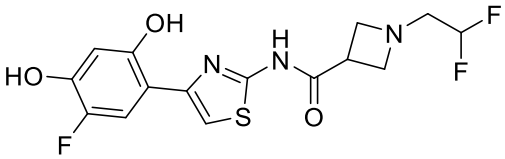
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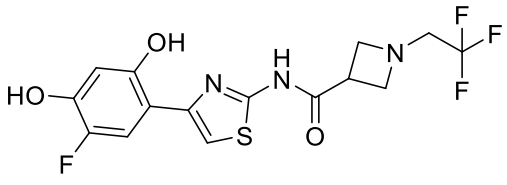
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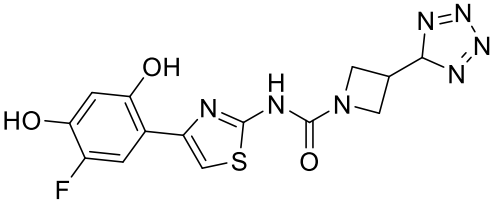
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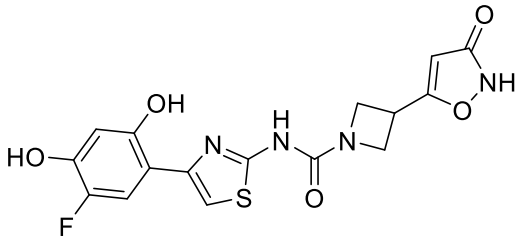
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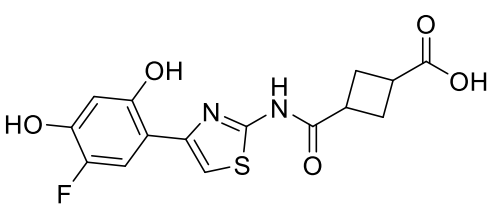
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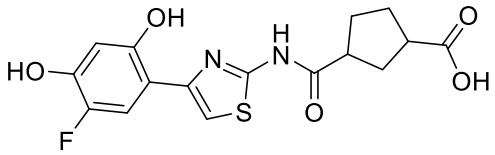
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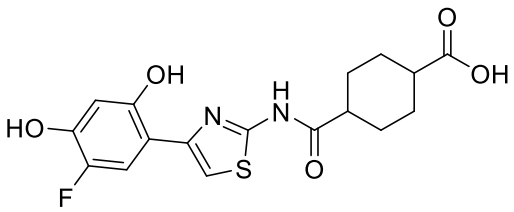
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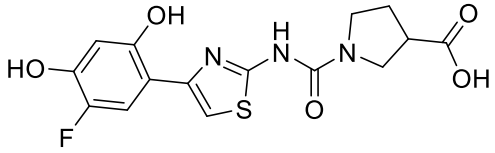
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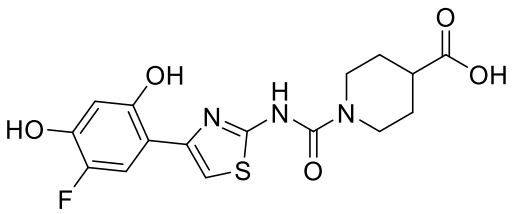
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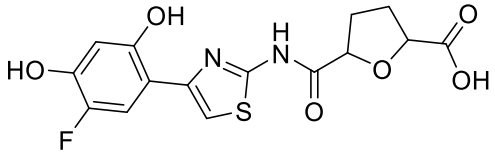
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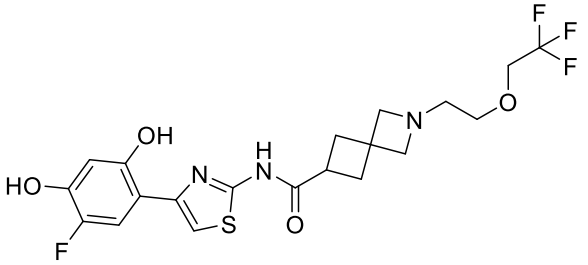
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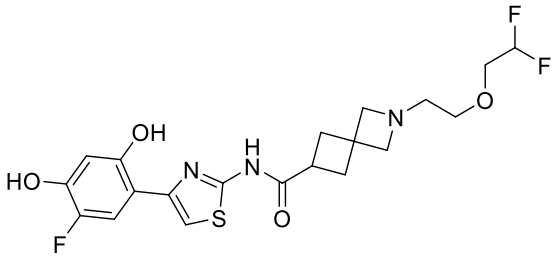
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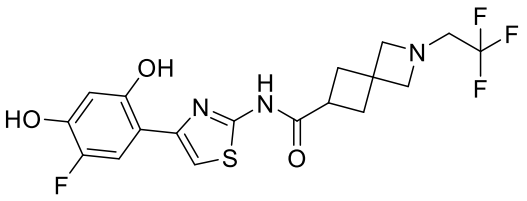
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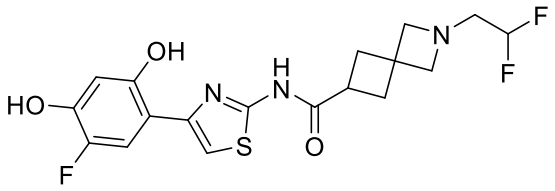
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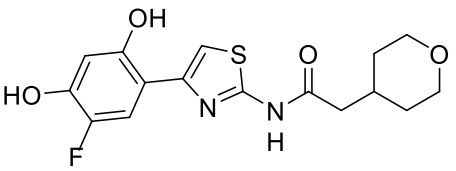
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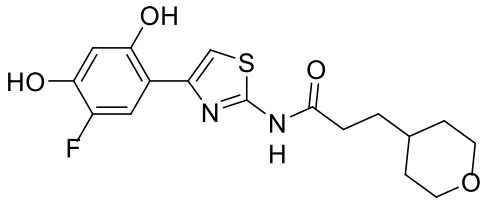
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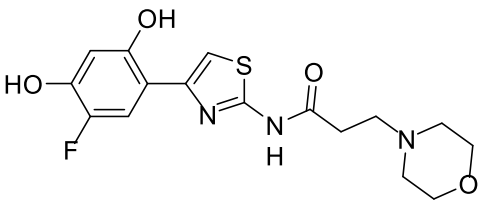
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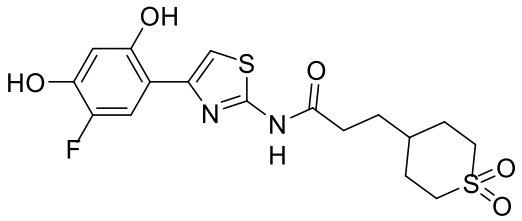
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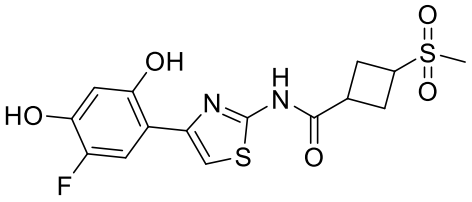
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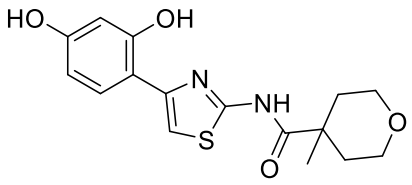
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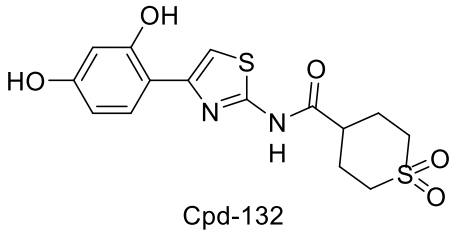
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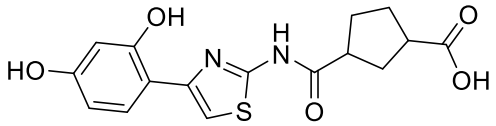
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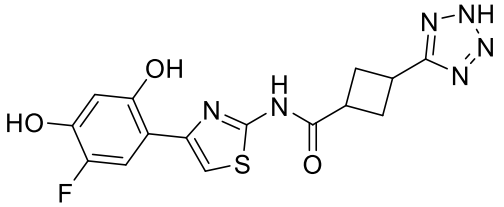
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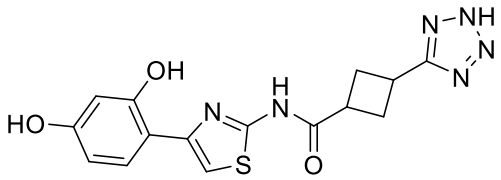
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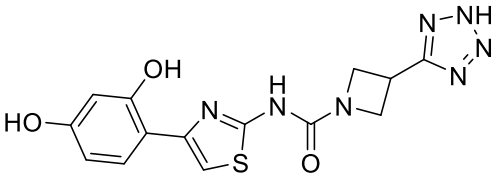
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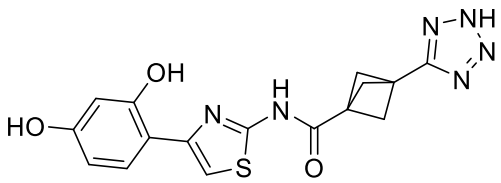
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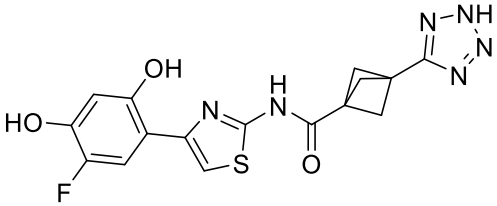
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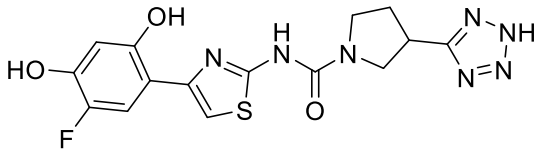
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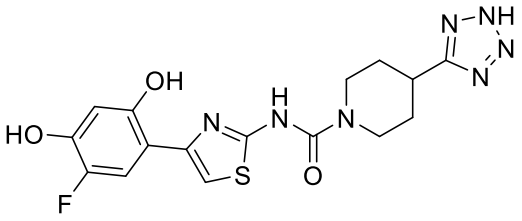
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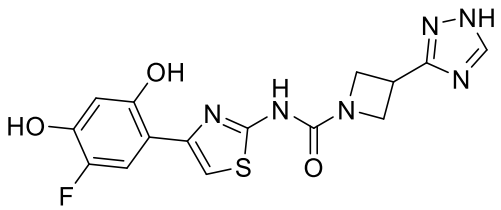
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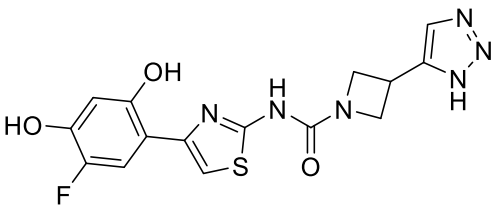
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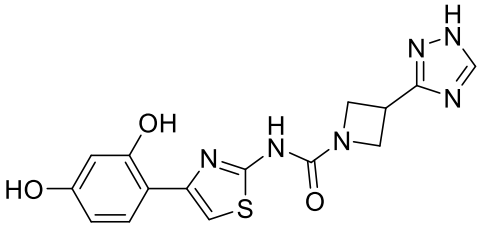
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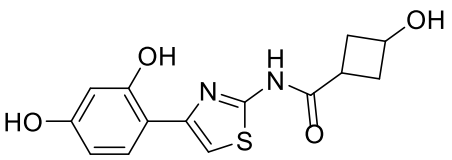


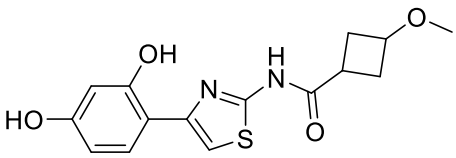
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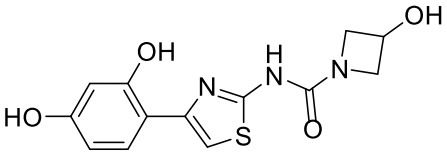


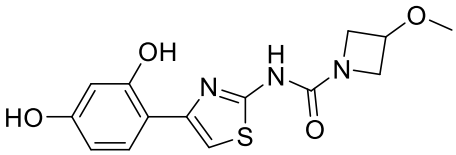
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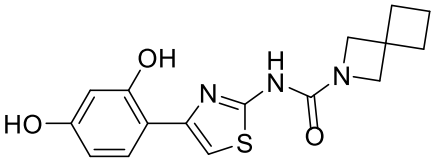


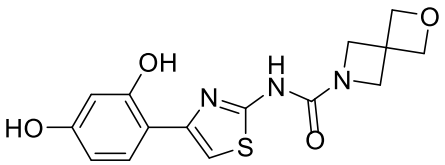
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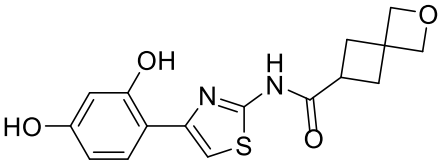
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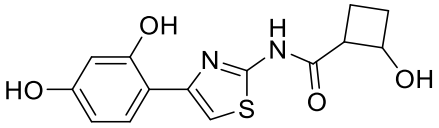
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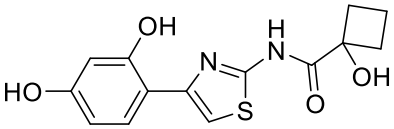
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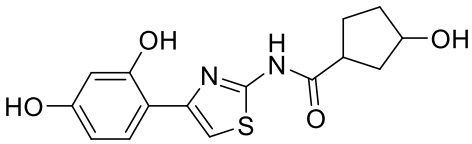
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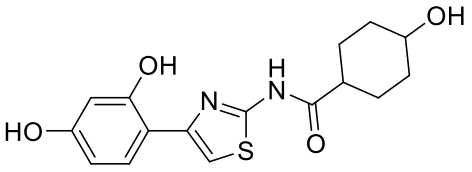
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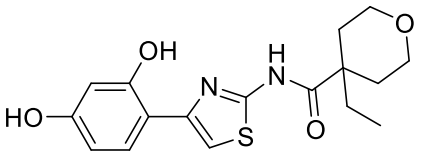
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Cpd-150 , 

Cpd-151 , 

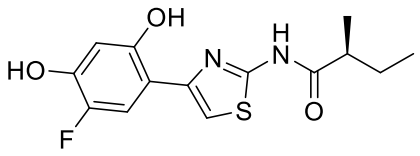
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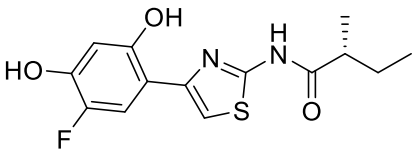
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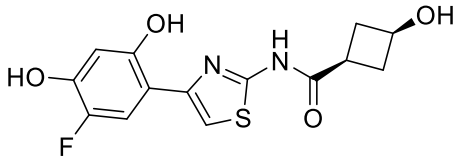
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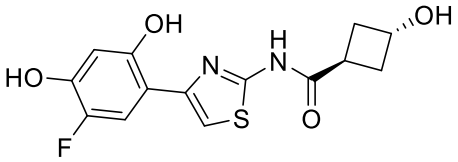
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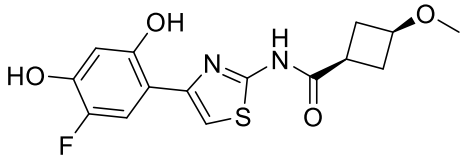
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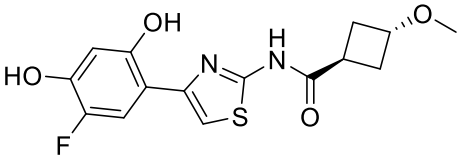
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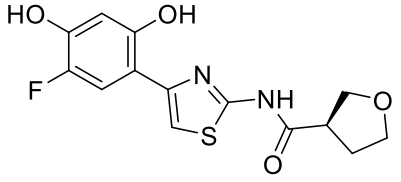
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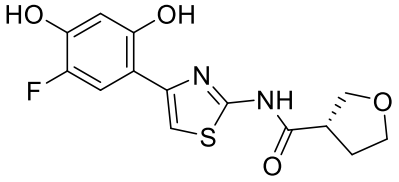
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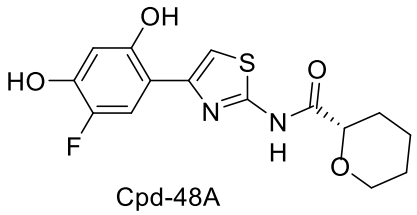
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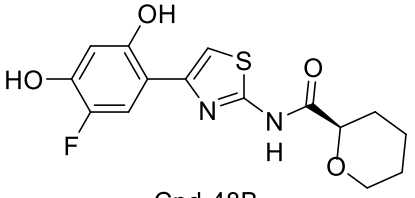
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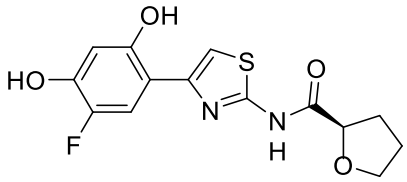
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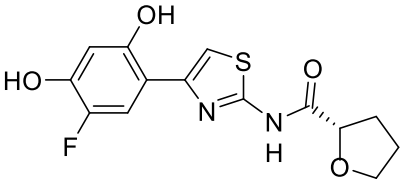
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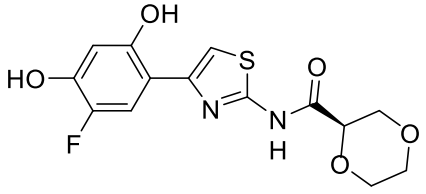
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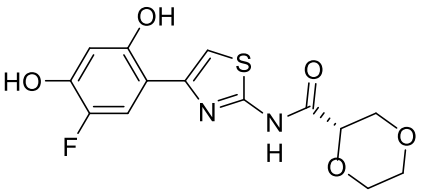
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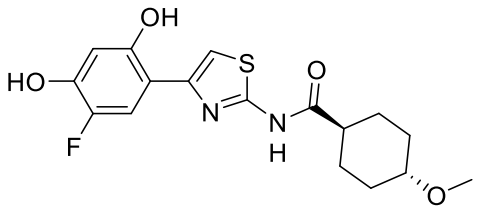
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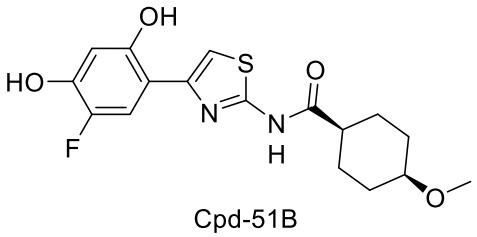


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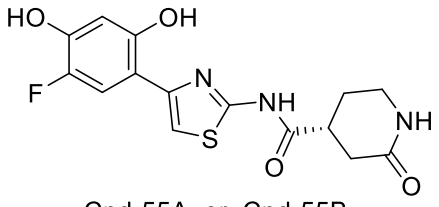
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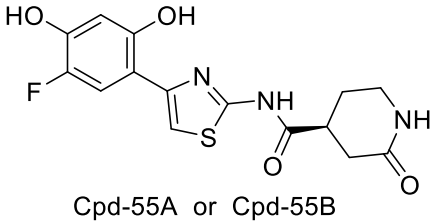
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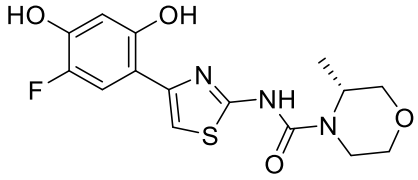
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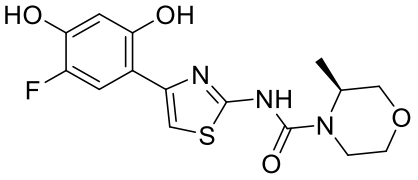
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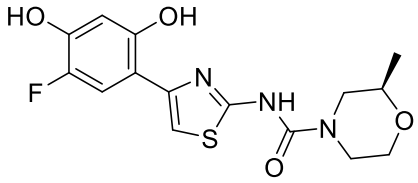
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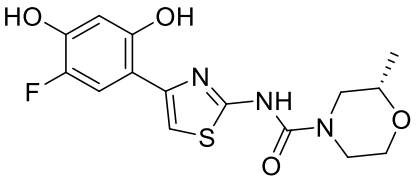
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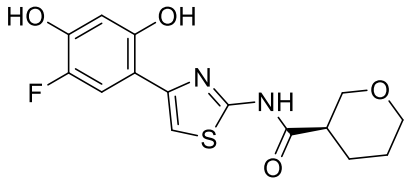
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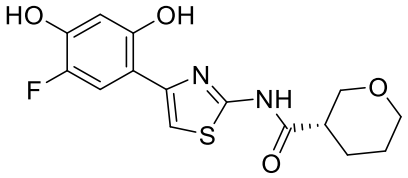
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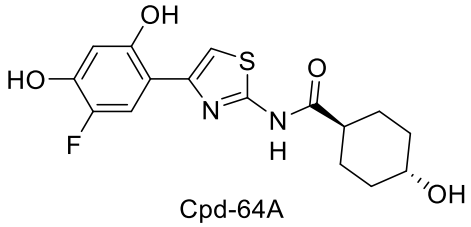
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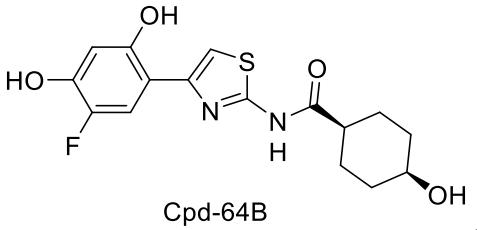
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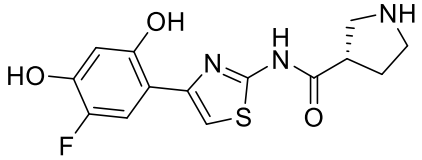
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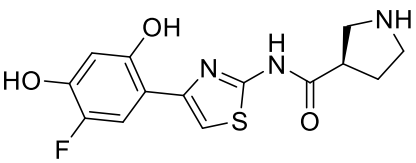
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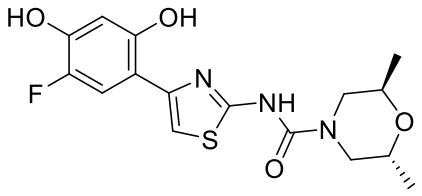
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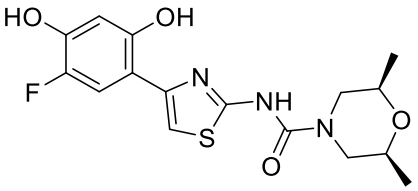


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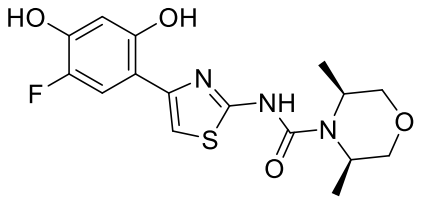


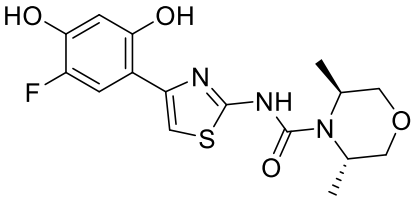
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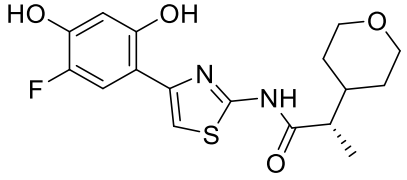
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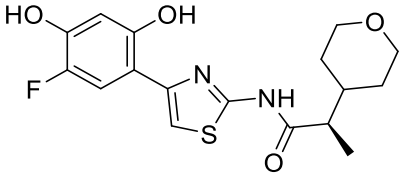
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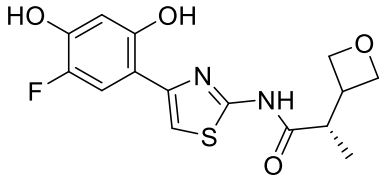
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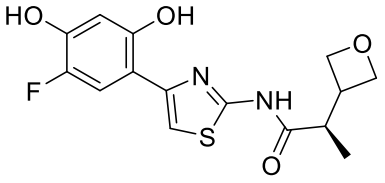
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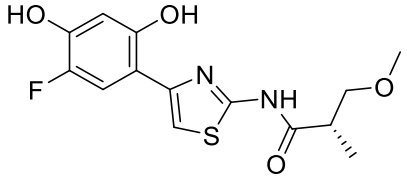
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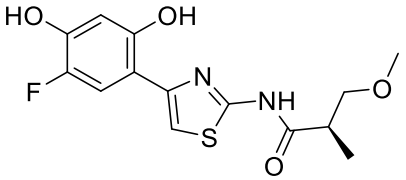
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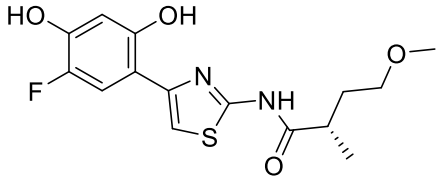
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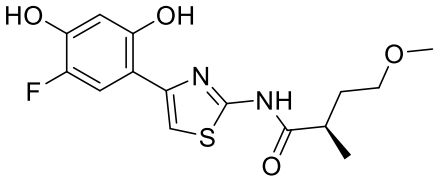
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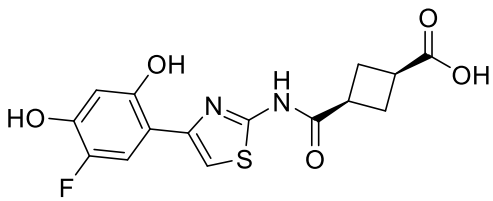
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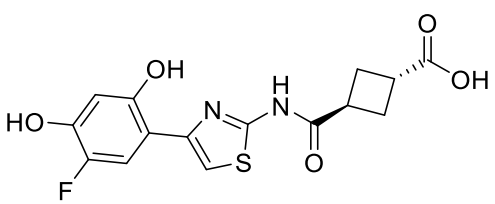
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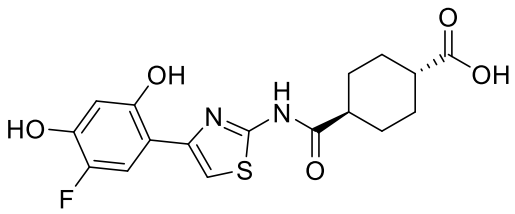
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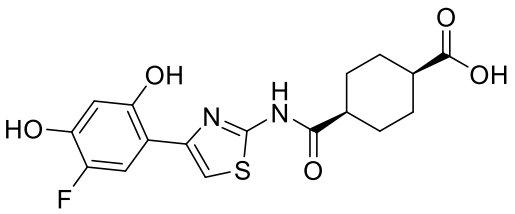
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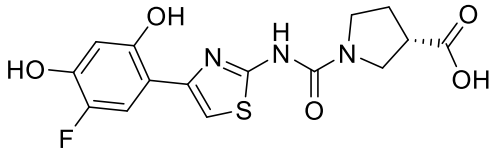
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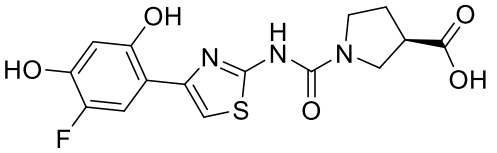
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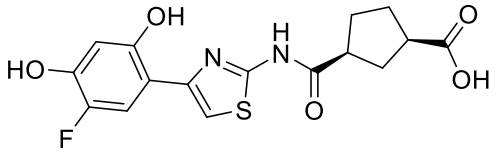
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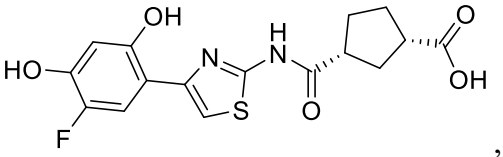
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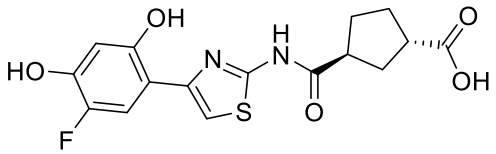
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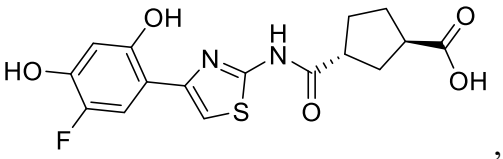
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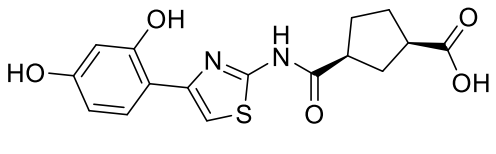
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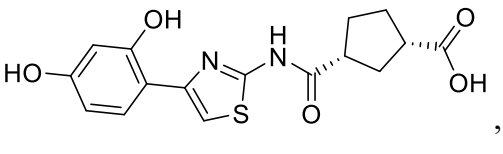
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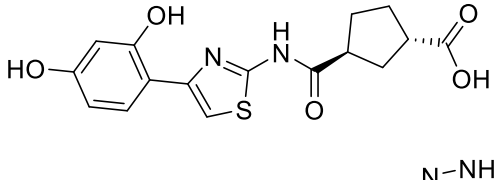
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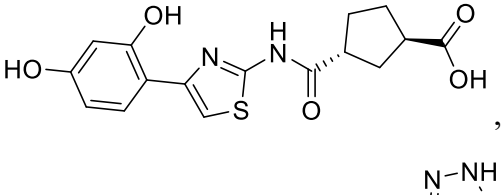
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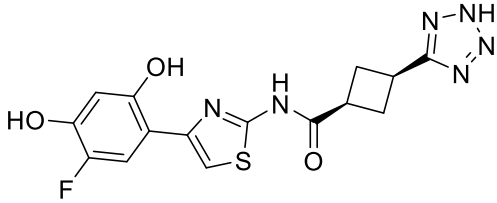
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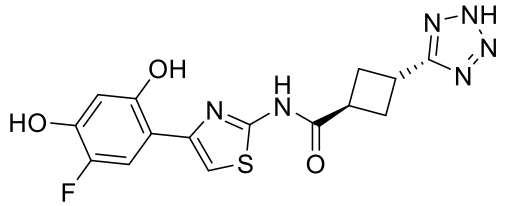
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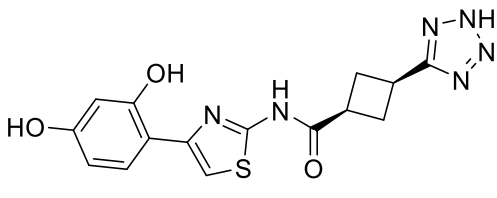
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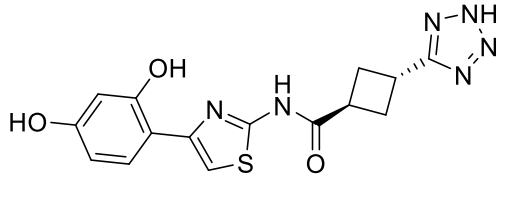
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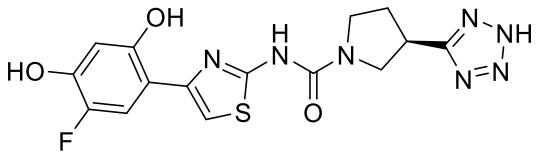
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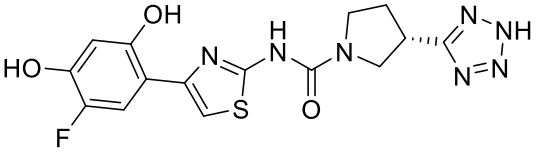
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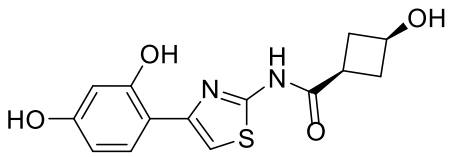
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Cpd-135A or Cpd-135B ,

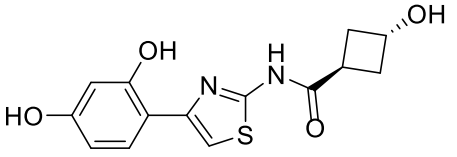


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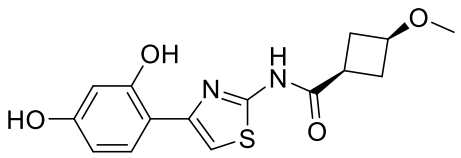
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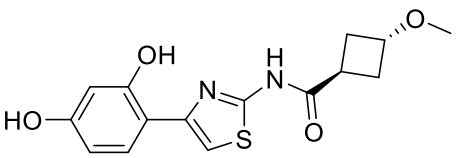
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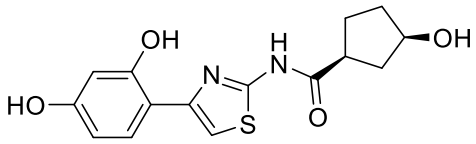
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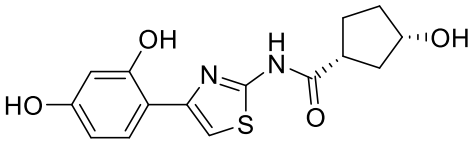
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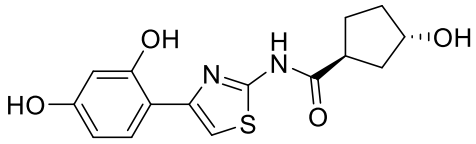
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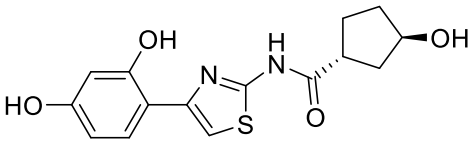
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Cpd-153A or Cpd-153B
or Cpd-153C or Cpd-153D ,



Cpd-153A or Cpd-153B
or Cpd-153C or Cpd-153D ,



Cpd-153A or Cpd-153B
or Cpd-153C or Cpd-153D .

The present invention further provides a pharmaceutical composition comprising a therapeutically effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof.

According to an embodiment of the present invention, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

According to an embodiment of the present invention, the pharmaceutical composition may further comprise one or more additional therapeutic agents.

The present invention further provides a method for treating tyrosinase-mediated skin pigmentation, which comprises administering to a patient a prophylactically or therapeutically effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof.

The present invention further provides a method for treating tyrosinase-mediated skin pigmentation, which comprises administering to a patient a prophylactically or therapeutically effective amount of the aforementioned pharmaceutical composition.

The symptoms of tyrosinase-mediated skin pigmentation are selected from chloasma, striae gravidarum, solar lentigines, café-au-lait spots, or freckles.

The tyrosinase-mediated skin pigmentation includes post-inflammatory pigmentation, wherein the inflammation is selected from acne, eczema, dermatitis, drug eruption, infection, sunburn, or trauma.

In some embodiment, the patient includes a mammal, preferably a human.

The present invention further provides at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof, or a pharmaceutical composition thereof, for use in treating tyrosinase-mediated diseases.

The present invention further provides the use of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof in the preparation of a drug.

According to embodiments of the present invention, the use may be the use in the preparation of a drug for treating conditions and/or diseases associated with tyrosinase-mediated skin pigmentation, such as the use in the preparation of tyrosinase inhibitor drugs.

According to embodiments of the present invention, the skin pigmentation disorders include chloasma, striae gravidarum, solar lentigines, café-au-lait spots, freckles, post-acne pigmentation, post-eczema pigmentation, post-dermatitis pigmentation, post-drug eruption pigmentation, post-infection pigmentation, post-sunburn pigmentation and post-traumatic pigmentation.

The present invention further provides a cosmetic composition comprising an effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or derivatives thereof.

According to embodiments of the present invention, the cosmetic composition further comprises one or more auxiliaries and/or additives, including thickeners, fillers, fragrances, colorants, emulsifiers, additional active ingredients such as vitamins or proteins, photoprotective agents, stabilizers, insect repellents, alcohols, water, salts, antibacterial agents, proteolytic or keratolytic active substances, and the like.

The present invention further provides a non-therapeutic cosmetic method, which comprises administering to a mammal in need thereof an effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, acceptable salts thereof or derivatives thereof, for ameliorating/adjuvantly treating the symptoms of tyrosinase-mediated skin pigmentation, or for skin whitening.

The present invention further provides a non-therapeutic cosmetic method, which comprises administering an effective amount of the cosmetic composition to a mammal in need thereof, for

ameliorating/adjuvantly treating the symptoms of tyrosinase-mediated skin pigmentation, or for skin whitening.

The symptoms of tyrosinase-mediated skin pigmentation are selected from chloasma, striae gravidarum, solar lentigines, café-au-lait spots, or freckles.

The tyrosinase-mediated skin pigmentation includes post-inflammatory pigmentation, wherein the inflammation is selected from acne, eczema, dermatitis, drug eruption, infection, sunburn, or trauma.

Beneficial Effects

The present invention obtains a novel class of compounds through structural optimization. These compounds not only exhibit excellent tyrosinase inhibitory activity and favorable physicochemical properties, but also can be used by target populations at an extremely low concentration, with no toxicity to melanocytes or the skin.

Definition and Explanation of Terms

Unless otherwise indicated, the definitions of groups and terms recorded in the specification and claims of the present application, including their definitions as examples, exemplary definitions, preferred definitions, definitions recorded in tables, definitions of specific compounds in examples, etc., may be arbitrarily combined and associated with each other. Such combined and associated group definitions and compound structures should be understood to be within the scope of the specification and/or claims of the present application.

Unless otherwise indicated, the numerical ranges recited in the present specification and claims are equivalent to at least reciting each specific integer value therein. For example, the numerical range “1-14” is equivalent to recording each integer value in the numerical range “1-14”, namely 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14.

The term “optional” (or “optionally”) in the general formula definitions of the present application means a situation of being substituted with zero, one or more substituents, for example “optionally substituted with one, two or more R” means that it may not be substituted with R (unsubstituted) or may be selectively substituted with one, two or more R.

“More” means three or more.

The term “carbon ring” refers to a saturated or unsaturated non-aromatic monocyclic or polycyclic (such as bicyclic) hydrocarbon ring (for example a monocyclic ring such as a cyclopropane ring, a cyclobutane ring, a cyclopentane ring, a cyclohexane ring, a cycloheptane ring, a cyclooctane ring, a cyclononane ring, or a bicyclic ring, including a spirocyclic, fused or bridged system (such as a bicyclo[1.1.1]pentane ring, a bicyclo[2.2.1]heptane ring, a bicyclo[3.2.1]octane ring or a bicyclo[5.2.0]nonane ring, a decalin ring), which may be optionally

substituted with 1 or more (such as 1, 2 or 3) suitable substituents. The term "3-6 membered carbon ring" refers to a carbon ring containing 3, 4, 5, or 6 ring-forming carbon atoms.

The term "C_{1-12} alkyl" is understood to mean linear and branched alkyl groups having 1 to 12 carbon atoms, "C_{1-8} alkyl" means linear and branched alkyl groups having 1, 2, 3, 4, 5, 6, 7, or 8 carbon atoms, and "C_{1-6} alkyl" means linear and branched alkyl groups having 1, 2, 3, 4, 5, or 6 carbon atoms. The alkyl is, for example, methyl, ethyl, propyl, butyl, amyl, hexyl, isopropyl, isobutyl, sec-butyl, tert-butyl, isoamyl, 2-methylbutyl, 1-methylbutyl, 1-ethylpropyl, 1,2-dimethylpropyl, neoamyl, 1,1-dimethylpropyl, 4-methylamyl, 3-methylamyl, 2-methylamyl, 1-methylamyl, 2-ethylbutyl, 1-ethylbutyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 2,3-dimethylbutyl, 1,3-dimethylbutyl or 1,2-dimethylbutyl, or isomers thereof.

The term "C_{3-12} cycloalkyl" should be understood to mean a saturated monovalent monocyclic, bicyclic (such as fused, bridged, spiro) hydrocarbon ring or tricyclic alkane having 3 to 12 carbon atoms, preferably "C_{3-10} cycloalkyl", more preferably "C_{3-8} cycloalkyl". The term "C_{3-12} cycloalkyl" should be understood to mean a saturated monovalent monocyclic, bicyclic (such as bridged, spiro) hydrocarbon ring or tricyclic alkane having 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. The C_{3-12} cycloalkyl may be a monocyclic hydrocarbon group, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, or a bicyclic hydrocarbon group, such as bornyl, indolyl, hexahydroindolyl, tetrahydronaphthyl, decahydronaphthyl, bicyclo[2.1.1]hexyl, bicyclo[2.2.1]heptyl, bicyclo[2.2.1]heptenyl, 6,6-dimethylbicyclo[3.1.1]heptyl, 2,6,6-trimethylbicyclo[3.1.1]heptyl, bicyclo[2.2.2]octyl, 2,7-diazaspiro[3,5]nonanyl, 2,6-diazaspiro[3,4]octanyl, or a tricyclic hydrocarbon group, such as adamantyl.

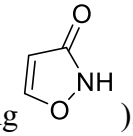
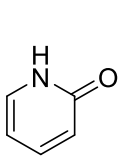
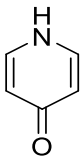
The term "C_{3-12} cycloalkenyl" should be understood to mean a monovalent monocyclic, bicyclic (such as fused, bridged, spiro) or tricyclic alkene containing a carbon-carbon double bond, and having 3 to 12 carbon atoms, preferably "C_{3-10} cycloalkenyl", more preferably "C_{3-8} cycloalkenyl", which may have 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 carbon atoms. The C_{3-12} cycloalkenyl may be a monocyclic hydrocarbon group, such as cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl or cyclodecenyl, or a bicyclic hydrocarbon group such as spiro[2.5]oct-5-enyl, spiro[3.5]non-6-enyl, spiro[4.5]dec-7-enyl.

The term "C_{6-14} aryl" should be understood to preferably mean a monovalent aromatic or partially aromatic monocyclic, bicyclic or tricyclic hydrocarbon ring having 6 to 14 carbon atoms, which may be a single aromatic ring or a fused polyaromatic ring, preferably "C_{6-10} aryl". The term "C_{6-14} aryl" should be understood as preferably representing a monovalent aromatic or partially aromatic monocyclic, bicyclic or tricyclic hydrocarbon ring ("C_{6-14} aryl") having 6, 7, 8, 9, 10, 11, 12, 13, or 14 carbon atoms, in particular a ring having 6 carbon atoms ("C_6 aryl"), such as a phenyl;

or biphenyl, or a ring having 9 carbon atoms ("C_9 aryl"), such as indanyl or indenyl, or a ring having 10 carbon atoms ("C_{10} aryl"), such as tetrahydronaphthyl, dihydronaphthyl, or naphthyl, or a ring having 13 carbon atoms ("C_{13} aryl"), such as fluorenyl, or a ring having 14 carbon atoms ("C_{14} aryl"), such as anthracenyl. When the C_{6-20} aryl is substituted, it can be monosubstituted or polysubstituted. Furthermore, there is no limitation on the substitution site, and for example, substitution may be at the ortho, para or meta position.

The term "5- to 14-membered heteroaryl" should be understood to include monovalent monocyclic, bicyclic (such as fused, bridged, spiro) or tricyclic aromatic ring systems which have 5 to 14 ring atoms and comprise 1 to 5 heteroatoms independently selected from N, O and S, for example "5- to 10-membered heteroaryl". The term "5- to 14-membered heteroaryl" should be understood to include monovalent monocyclic, bicyclic or tricyclic aromatic ring systems, which have 5, 6, 7, 8, 9, 10, 11, 12, 13 or 14 ring atoms, in particular 5 or 6 or 9 or 10 carbon atoms, and comprise 1 to 5, preferably 1 to 3 heteroatoms that are each independently selected from N, O and S, and which, in addition, in each case may be benzo-fused. "Heteroaryl" also means a group in which a heteroaromatic ring is fused with one or more aryl, alicyclic, or heterocyclic rings, wherein the radical or site of attachment is on the heteroaromatic ring. Non-limiting examples include 1-, 2-, 3-, 5-, 6-, 7- or 8-indolizinyl, 1-, 3-, 4-, 5-, 6-, or 7-isoindolyl, 2-, 3-, 4-, 5-, 6- or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-indazolyl, 2-, 4-, 5-, 6-, 7- or 8-purinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8- or 9-quinolizinyl, 2-, 3- , 4-, 5-, 6-, 7- or 8-quinolinyl, 1-, 3-, 4-, 5-, 6-, 7- or 8-isoquinolinyl, 1-, 4-, 5-, 6-, 7- or 8-phthalazinyl, 2-, 3-, 4-, 5- or 6-naphthyridinyl, 2-, 3-, 5-, 6-, 7- or 8-quinazolinyl, 3-, 4-, 5-, 6-, 7- or 8-cinnolinyl, 2-, 4-, 6- or 7-pteridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-4aH carbazolyl, 1-, 2-, 3-, 4-, 5-, 6-, 7- or 8-carbazolyl, 1-, 3-, 4-, 5-, 6-, 7-, 8- or 9-carbolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenanthridinyl, 1-, 2-, 3-, 4-, 5-, 6-, 7-, 8- or 9-acridinyl, 1-, 2-, 4-, 5-, 6-, 7-, 8- or 9-pyridyl, 2-, 3-, 4-, 5-, 6-, 8-, 9- or 10-phenanthrolinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8- or 9-phenazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenothiazinyl, 1-, 2-, 3-, 4-, 6-, 7-, 8-, 9- or 10-phenazinyl, 2-, 3-, 4-, 5-, 6- or 1-, 3-, 4-, 5-, 6-, 7-, 8-, 9- or 10-benzoisoquinolyl, 2-, 3-, 4- or thieno[2,3-b]furanyl, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- or 11-7H-pyrazino[2,3-c]carbazolyl, 2-, 3-, 5-, 6- or 7-2H-furo[3,2-b]pyranyl, 2-, 3-, 4-, 5-, 7-, or 8-5H-pyridino[2,3-d]-o-oxazinyl, 1-, 3-, or 5-1H-pyrazolo[4,3-d]-oxazolyl, 2-, 4-, or 54H-imidazo[4,5-d]thiazolyl, 3-, 5-, or 8-pyrazino[2,3-d]pyridazinyl, 2-, 3-, 5-, or 6-imidazo[2,1-b]thiazolyl, 1-, 3-, 6-, 7-, 8-, or 9-furo[3,4-c]cinnolinyl, 1-, 2-, 3-, 4-, 5-, 6-, 8-, 9-, 10 or 11-4H-pyridino[2,3-c]carbazolyl, 2-, 3-, 6- or 7-imidazo[1,2-b][1,2,4]triazinyl, 7-benzo[b]thienyl, 2-, 4-, 5-, 6- or 7-benzoxazolyl, 2-, 4-, 5-, 6- or 7-benzimidazolyl, 2-, 4- , 4-, 5-, 6- or 7-benzothiazolyl, 1-, 2-, 4-, 5-, 6-, 7-, 8- or 9-benzoxapinyl, 2-, 4-, 5-, 6-, 7- or 8-benzoxazinyl, 1-, 2-, 3-, 5-, 6-, 7-, 8-, 9-, 10- or 11-4H-pyrrolo[1,2-b][2]benzazapinyl. A typical fused heteroaryl includes, but is not limited to, 2-, 3-, 4-, 5-, 6-, 7-, or 8-quinolyl, 1-, 3-, 4-, 5-, 6-, 7-, or 8-isoquinolyl, 2-, 3-, 4-, 5-, 6-,

or 7-indolyl, 2-, 3-, 4-, 5-, 6-, or 7-benzo[b]thienyl, 2-, 4-, 5-, 6-, or 7-benzoxazolyl, 2-, 4-, 5-, 6-, or 7-benzimidazolyl, and 2-, 4-, 5-, 6-, or 7-benzothiazolyl. When the 5- to 14-membered heteroaryl is linked to other groups to constitute the compound of the present invention, either the carbon atom on the 5- to 14-membered heteroaryl ring can be linked to other groups, or the heteroatom on the 5- to 14-membered heteroaryl ring can be linked to other groups. When the 5- to 14-membered heteroaryl is substituted, it can be monosubstituted or polysubstituted. Further, the substitution site is not limited. For example, hydrogen attached to a carbon atom on the heteroaryl ring may be substituted, or hydrogen attached to a heteroatom on the heteroaryl ring may be substituted.

The term "5- to 6-membered heteroaromatic ring" shall be understood to mean a monovalent monocyclic ring having 5 or 6 ring atoms and containing 1 to 5, preferably 1 to 3, heteroatoms independently selected from N, O and S. Examples include pyrazole ring, thiophene ring, furan ring, imidazole ring, thiazole ring, oxazole ring, isoxazole ring, isoxazolone ring (e.g., isoxazol-3(2*H*)-one ring ), pyrimidine ring, pyridine ring, pyridone ring (e.g.,  , ), pyrazine ring, pyridazine ring, and the like. When the 5- to 6-membered heteroaromatic ring is linked to other groups to constitute the compound of the present invention, either the carbon atom on the 5- to 6-membered heteroaromatic ring can be linked to other groups, or the heteroatom on the 5- to 6-membered heteroaromatic ring can be linked to other groups. When the 5- to 6-membered heteroaromatic ring is substituted, it can be monosubstituted or polysubstituted. Further, the substitution site is not limited. For example, hydrogen attached to a carbon atom on the heteroaromatic ring may be substituted, or hydrogen attached to a heteroatom on the heteroaromatic ring may be substituted.

Unless otherwise defined, the term "3- to 14-membered heterocyclyl" refers to a saturated or unsaturated non-aromatic ring or ring system, for example, a 4-, 5-, 6- or 7-membered monocyclic ring, a 7-, 8-, 9-, 10-, 11- or 12-membered bicyclic ring (e.g. fused, bridged, spiro) or a 10-, 11-, 12-, 13- or 14-membered tricyclic ring system, and contains at least one, for example 1, 2, 3, 4, 5 or more heteroatoms selected from O, S and N, wherein N and S may also be optionally oxidized to various oxidation states to form nitrogen oxides, -S(O)- or -$S(O)_2$-. Preferably, the heterocyclyl may be selected from "3- to 10-membered heterocyclyl". The term "3- to 10-membered heterocyclyl" means a saturated or unsaturated non-aromatic ring or ring system and contains at least one heteroatom selected from O, S and N. The heterocyclyl may be linked to the rest of the molecule via any of its carbon atoms or nitrogen atoms (if present). The heterocyclyl may include a fused or bridged ring and a spirocyclic ring. In particular, the heterocyclyl may include, but is not limited to: a 4-membered ring, such as azetidinyl, oxetanyl; a 5-membered ring, such as

tetrahydrofuranyl, dioxolyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, pyrrolinyl; or a 6-membered ring, such as tetrahydropyranyl, piperidinyl, morpholinyl, dithianyl, thiomorpholinyl, piperazinyl or trithianyl; or a 7-membered ring, such as diazepanyl. Optionally, the heterocyclyl may be benzo-fused. The heterocyclyl may be bicyclic, such as but not limited to a 5,5-membered ring, such as a hexahydrocyclopenta[c]pyrrol-2(1H)-yl ring, or a 5,6-membered bicyclic ring, such as a hexahydropyrrolo[1,2-a]pyrazin-2(1H)-yl ring. The heterocyclyl may be partially unsaturated, that is, it may contain one or more double bonds, such as but not limited to dihydrofuranyl, dihydropyranyl, 2,5-dihydro-1H-pyrrolyl, 4H-[1,3,4]thiadiazinyl, 1,2,3,5-tetrahydrooxazolyl or 4H-[1,4]thiazinyl, or it may be benzo-fused, such as but not limited to dihydroisoquinolinyl. When the 3- to 14-membered heterocyclyl is linked to other groups to constitute the compound of the present invention, either the carbon atom on the 3- to 14-membered heterocyclyl can be linked to other groups, or the heterocyclic atom on the 3- to 14-membered heterocyclyl can be linked to other groups. For example, when the 3- to 14-membered heterocyclyl is selected from piperazinyl, the nitrogen atom on the piperazinyl may be linked to other groups. Alternatively, when the 3- to 14-membered heterocyclyl is selected from piperidinyl, the nitrogen atom on the piperidinyl ring and the carbon atom at the para position thereof may be linked to other groups.

The term “spiro ring” refers to a ring system in which two rings share one ring atom.

The term “fused ring” refers to a ring system in which two rings share 2 ring atoms.

The term “bridged ring” refers to a ring system in which two rings share 3 or more ring-forming atoms.

The term “halogen” represents fluorine, chlorine, bromine, and iodine.

“Halo” means being substituted with one or more halogens.

In the present invention, the compound involved also comprises an isotopically labeled compound, which is the same as the compound of formula I, but in which one or more atoms are replaced by atoms having an atomic mass or mass number different from the atomic mass or mass number usually occurring in nature. Exemplary isotopes that can be incorporated into the compound of the present invention comprise isotopes of H, C, N, O, S, F and Cl, such as ^{2}H, ^{3}H, ^{13}C, ^{11}C, ^{14}C, ^{15}N, ^{18}O, ^{17}O, ^{32}P, ^{35}S, ^{18}F and ^{36}Cl. The compound of the present invention containing the aforementioned isotopes and/or other isotopes of other atoms and a prodrug thereof, or a pharmaceutically acceptable salt of the compound or the prodrug are covered in the scope of the present invention. Some isotopically labeled compounds of the present invention, for example, compounds incorporated with radioactive isotopes (such as ^{3}H and ^{14}C) can be used in the distribution determination of drugs and/or substrates in tissues. The isotopes tritium (that is, ^{3}H) and carbon 14 (that is, ^{14}C) are particularly preferred because of their easy preparation and detectability. Furthermore, the substitution with a heavier isotope (such as deuterium, that is, ^{2}H or

D) can provide some therapeutic advantages due to the greater metabolic stability (for example, increased in-vivo half-life or reduced dosage requirement), and is thus preferred in some cases. The compound of the present invention as claimed in the claims can be particularly defined to be substituted with deuterium or tritium. In addition, in case that hydrogen in a substituent is not explicitly indicated to be deuterium or tritium, it does not mean that deuterium or tritium is excluded, but deuterium or tritium can be contained as well.

Those skilled in the art will appreciate that the compound represented by formula (I) may exist in the form of various pharmaceutically acceptable salts. If the compounds have basic centers, they can form acid addition salts; if they have acidic centers, they can form base addition salts; if the compounds contain both acidic centers (e.g. carboxyl) and basic centers (e.g. amino), they can also form inner salts.

The compounds of the present invention may be present in the form of solvates, such as hydrates, wherein the compounds of the present invention comprise polar solvents, such as water, methanol or ethanol, as structural elements of the lattice of the compounds. The polar solvent, especially water, may be present in a stoichiometric or non-stoichiometric amount.

Depending on their molecular structure, the compounds of the present invention may be chiral and may therefore exist in various enantiomeric forms. These compounds may therefore exist in racemic or optically active forms. The compounds of the present invention encompass isomers in which the chiral carbons are each in R or S configuration, or mixtures and racemates thereof. The compounds of the present invention or their intermediates can be separated into enantiomeric compounds by chemical or physical methods known to those skilled in the art, or used in synthesis in this form. In the case of racemic amines, diastereomers are prepared from the mixture by reaction with an optically active resolving reagent. Examples of suitable resolving reagents are optically active acids, such as the R and S forms of tartaric acid, diacetyltartaric acid, dibenzoyltartaric acid, mandelic acid, malic acid, lactic acid, appropriate N-protected amino acids (e.g. N-benzoylproline or N-phenylsulfonylproline) or various optically active camphorsulfonic acids. Chromatographic enantiomeric resolution can also be advantageously carried out by means of optically active resolving reagents, such as dinitrobenzoylphenylglycine, cellulose triacetate or other carbohydrate derivatives or chirally derivatized methacrylate polymers immobilized on silica gel. Suitable eluents for this purpose are aqueous or alcoholic solvent mixtures, for example, hexane/isopropanol/acetonitrile.

The corresponding stable isomers can be separated according to known methods, such as by extraction, filtration or column chromatography.

The term “patient” refers to any animal, including mammals, preferably mice, rats, other rodents, rabbits, dogs, cats, pigs, cows, sheep, horses or primates, and most preferably humans.

The term “therapeutically effective amount” refers to the amount of an active compound or drug which causes a biological or medical response sought by a researcher, veterinarian, physician or other clinician in a tissue, system, animal, individual or human, and which comprises one or more of the following: (1) prevention of disease: for example, prevention of a disease, disorder or condition in an individual who is susceptible to the disease, disorder or condition but has not yet experienced or developed the pathology or symptoms of the disease. (2) Inhibition of disease: for example, inhibition of a disease, disorder or condition (i.e., prevention of further progression of pathology and/or symptoms) in an individual undergoing or exhibiting the pathology or symptoms of the disease, disorder or condition. (3) Alleviation of disease: for example, alleviation of a disease, disorder or condition (i.e., reversion of pathology and/or symptoms) in an individual undergoing or exhibiting the pathology or symptoms of the disease, disorder or condition.

DETAILED DESCRIPTION

The technical solution of the present invention will be further described in detail below in conjunction with specific examples. It should be understood that the following examples are only intended to exemplify and explain the present invention and should not be construed as limiting the scope of protection of the present invention. All technologies realized based on the above contents of the present invention are included in the scope that the present invention intends to protect.

Unless otherwise indicated, the raw materials and reagents used in the following examples are commercially available or may be prepared by known methods.

The structures of the compounds in the present invention are determined by nuclear magnetic resonance (NMR) or/and liquid chromatography-mass spectrometry (LC-MS). NMR chemical shifts (δ) are given in parts per million (ppm). The NMR measurement is performed by using Bruker AVANCE-400 nuclear magnetic resonance spectrometer, with deuterated dimethyl sulfoxide (DMSO-*d6*), deuterated methanol (CD_3OD), and deuterated chloroform ($CDCl_3$) as determination solvents, and with tetramethylsilane (TMS) as an internal standard.

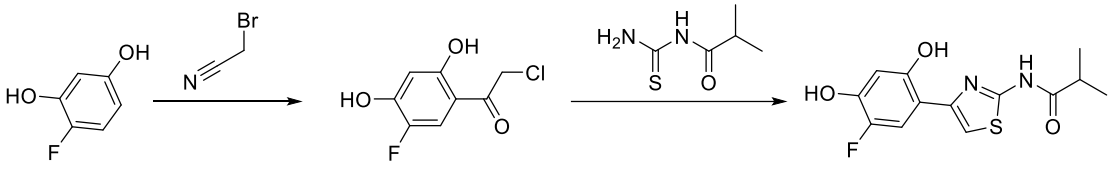
An Agilent 1200 Infinity Series mass spectrometer is used for liquid chromatography-mass spectrometry (LC-MS) measurements. HPLC analysis is performed using an Agilent 1200DAD high pressure liquid chromatograph (Sunfire C18 150×4.6 mm column) and a Waters 2695-2996 high pressure liquid chromatograph (Gimini C18 150×4.6 mm column).

Yantai Huanghai HSGF254 or Qingdao GF254 silica gel plate is used as the silica gel plate for chromatography, the specification used for TLC is from 0.15 mm to 0.20 mm, and the specification of the thin layer chromatography for separation and purification of products is from 0.4 mm to 0.5 mm. Yantai Huanghai silica gel of 200-300 mesh is generally used as the carrier for column chromatography.

Unless otherwise specified, all reactions in the present invention are carried out under continuous magnetic stirring in a dry nitrogen or argon atmosphere in a dry solvent at a reaction temperature expressed in °C.

Example 1

Preparation of N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide **Cpd-01**



Cpd-01a Cpd-01b Cpd-01

Step 1 Preparation of 2-chlo-1-(5-fluoro-2,4-dihydroxyphenyl)ethan-1-one

4-Fluorobenzene-1,3-diol Cpd-01a (500 mg, 3.90 mmol), bromoacetonitrile (515 mg, 4.29 mmol) and zinc chloride (266 mg, 1.95 mmol) were dissolved in hydrochloric acid/dioxane (4 M, 10 mL). The mixture was stirred at 45°C for 16 h. Afterwards, water (10 mL) was added, and the temperature was raised to 70°C with continuous stirring for 3 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature, extracted with ethyl acetate, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, and concentrated to afford crude 2-chloro-1-(5-fluoro-2,4-dihydroxyphenyl)ethan-1-one Cpd-01b (400 mg, pale yellow solid), with a yield of 45%.

MS m/z (ESI): 205.1(M+1)

Step 2 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide

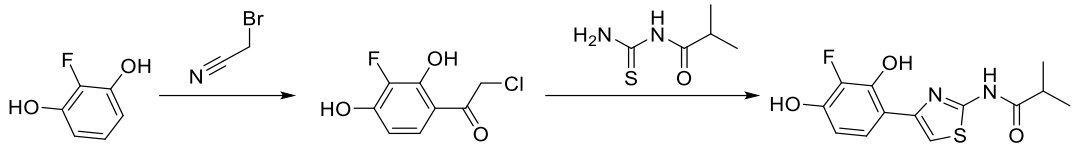
2-Chloro-1-(5-fluoro-2,4-dihydroxyphenyl)ethan-1-one Cpd-01b (400 mg, 1.95 mmol) and 2-isopropylcarbonylthiourea (286 mg, 1.95 mmol) were dissolved in ethanol solution (5 mL). The reaction mixture was stirred at 85°C for 3 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford the product *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide **Cpd-01** (32 mg), with a yield of 5.5%.

MS m/z (ESI): 297.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.16 (s, 1H), 10.66 (s, 1H), 9.96 (s, 1H), 7.63 (d, *J* = 12.8 Hz, 1H), 7.52 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 2.79 - 2.71 (m, 1H),1.13 (d, *J* = 6.9 Hz, 6H).

Example 2

Preparation of *N*-(4-(3-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide **Cpd-02**



Cpd-02a Cpd-02b Cpd-02

Step 1 Preparation of 2-chloro-1-(3-fluoro-2,4-dihydroxyphenyl)ethan-1-one

2-Fluorobenzene-1,3-diol Cpd-02a (500 mg, 3.90 mmol), bromoacetonitrile (515 mg, 4.29 mmol) and zinc chloride (266 mg, 1.95 mmol) were dissolved in hydrochloric acid/dioxane (4 M, 10 mL). The mixture was stirred at 45°C for 16 h. Afterwards, water (10 mL) was added, and the temperature was raised to 70°C with continuous stirring for 3 h. Upon completion of the reaction, the reaction mixture was cooled to room temperature, extracted with ethyl acetate, and washed with saturated brine. The organic phase was dried over anhydrous sodium sulfate, and concentrated to afford crude 2-chloro-1-(3-fluoro-2,4-dihydroxyphenyl)ethan-1-one **Cpd-02b** (500 mg, pale yellow solid), which was directly used in the next step.

Step 2 Preparation of N-(4-(3-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide

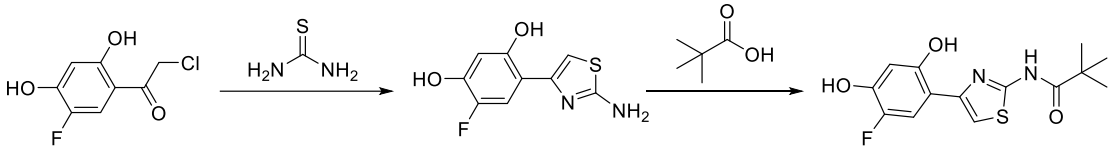
The crude 2-chloro-1-(3-fluoro-2,4-dihydroxyphenyl)ethan-1-one **Cpd-02b** (500 mg) and 2-isopropylcarbonylthiourea (300 mg, 2.05 mmol) were dissolved in ethanol solution (5 mL). The reaction mixture was stirred at 85°C for 3 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford the product *N*-(4-(3-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)isobutyramide **Cpd-02** (34 mg), with a yield of 2.9% over two steps.

MS m/z (ESI): 297.1(M+1)

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.56 (s, 1H), 7.27 (d, J = 2.0 Hz, 0.5H), 7.25 (d, J = 2.0 Hz, 0.5H), 7.06 (s, 1H), 6.57 (t, J = 4.0 Hz, 1H), 2.79 - 2.72 (m, 1H), 1.34 (d, J = 6.9 Hz, 6H).

Example 3

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)pivalamide **Cpd-03**



Cpd-01b Cpd-01c Cpd-03

Step 1 Preparation of 4-(2-aminothiazol-4-yl)-6-fluorobenzene-1,3-diol **Cpd-01c**

Cpd-01b (35 g crude product) and thiourea (6.6 g, 0.087 mol) were dissolved in dioxane solution (100 mL). The reaction mixture was stirred at 90°C for 16 h. After completion of the

reaction, the mixture was cooled to room temperature and then filtered. The filter cake was dissolved in a large amount of sodium bicarbonate solution, followed by extraction with ethyl acetate. The organic phase was washed with saturated aqueous sodium bicarbonate solution, dried and concentrated to afford the product **Cpd-01c** (6.2 g, white solid).

MS m/z (ESI): 227.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.69 (s, 1H), 9.88 (s, 1H), 7.52 – 7.37 (m, 3H), 7.40 (s, 1H), 6.90 (s, 1H).

Step 2 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)pivalamide **Cpd-03**

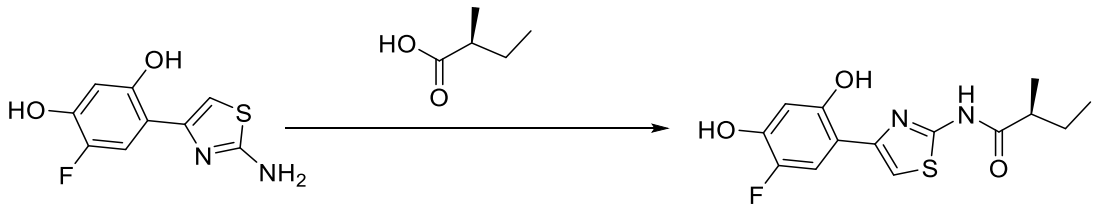
Cpd-01c (60 mg, 0.26 mmol), pivalic acid (162.5 mg, 1.59 mmol), BOP reagent (703.8 mg, 1.59 mmol) and *N,N*-diisopropylethylamine (274.2 mg, 2.1216 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 16 h. After the reaction was completed, the temperature was lowered to 45°C, and aqueous sodium hydroxide solution (8 mol/L, 1 mL) was added. The reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, dilute hydrochloric acid solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-03** (32.93 mg), with a yield of 40.01%.

MS m/z (ESI): 311.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.78 (s, 1H), 10.79 (s, 1H), 9.95 (s, 1H), 7.66 (d, *J* = 12.8 Hz, 1H), 7.51 (s, 1H), 6.49 (d, *J* = 7.9 Hz, 1H), 1.26 (s, 9H).

Example 4

Preparation of (*S*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-2-methylbutanamide **Cpd-04A**



Cpd-01c (60 mg, 0.26 mmol), (*S*)-2-methylbutanoic acid (162.5 mg, 1.59 mmol), BOP reagent (703.8 mg, 1.59 mmol) and *N,N*-diisopropylethylamine (274.2 mg, 2.1216 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 16 h. After the reaction was completed, the temperature was lowered to 45°C, and aqueous sodium hydroxide solution (8 mol/L, 1 mL) was added. The reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, dilute hydrochloric acid solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and

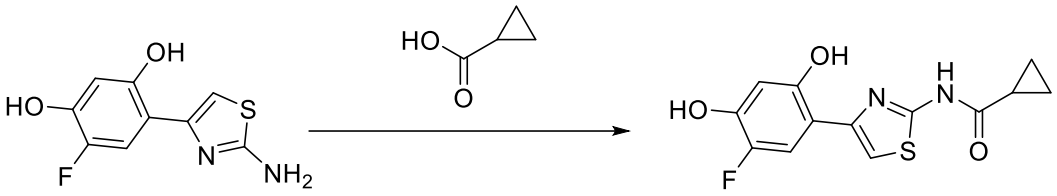
concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-04A** (35.47 mg), with a yield of 43.10%.

MS m/z (ESI): 311.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.18 (s, 1H), 10.65 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 2.58 (dd, J = 14.1, 6.6Hz, 1H), 1.71 – 1.57 (m, 1H), 1.46 (dd, J = 14.1, 6.8 Hz, 1H), 1.12 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H).

Example 5

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)cyclopropanecarboxamide **Cpd-09**



Cpd-01c Cpd-09

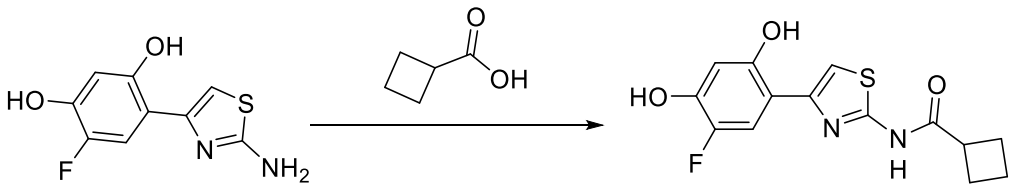
Cpd-01c (100 mg, 0.44 mmol), cyclopropanecarboxylic acid (227 mg, 2.64 mmol), BOP reagent (1168 mg, 2.64 mmol) and *N,N*-diisopropylethylamine (1135 mg, 8.80 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 6 h. After the reaction was completed, the temperature was lowered to 45°C, and aqueous sodium hydroxide solution (6 mol/L, 5 mL) was added. The reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-09** (20 mg), with a yield of 16%.

MS m/z (ESI): 295.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.49 (s, 1H), 10.63 (s, 1H), 9.96 (s, 1H), 7.63 (d, *J* = 12.4 Hz, 1H), 7.50 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 1.99 - 1.91 (m, 1H), 0.95 - 0.85 (m, 4H).

Example 6

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)cyclobutanecarboxamide **Cpd-11**



Cpd-01c Cpd-11

Cpd-01c (100 mg, 0.44 mmol) was dissolved in N,N-dimethylformamide solution (5 mL), followed by the addition of cyclobutanecarboxylic acid (265 mg, 2.65 mmol), BOP reagent (1171

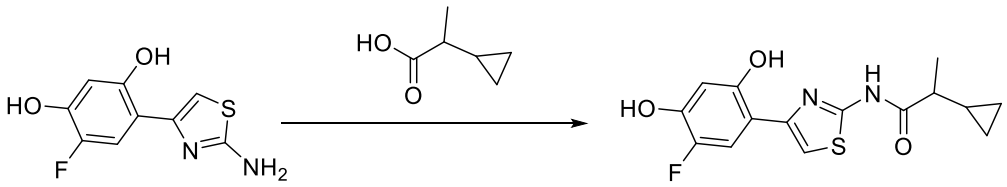
mg, 2.65 mmol) and N,N-diisopropylethylamine (568 mg, 4.4 mmol). The reaction mixture was stirred at 55°C for 16 h. Upon completion of the reaction, the mixture was poured into water (20 mL) and extracted with ethyl acetate (10 mL × 2). The organic phase was concentrated to dryness to afford the crude product as a brown oil. The crude product was dissolved in methanolic ammonia solution, and the reaction mixture was stirred at 25°C for 1 h. After the reaction was completed, the reaction mixture was concentrated to afford a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford the product **Cpd-11** (54 mg), with a yield of 40%.

MS m/z (ESI): 309.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 10.67 (s, 1H), 9.95 (s, 1H), 7.62 (d, *J* = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 3.42 – 3.34 (m, 1H), 2.33 – 2.10 (m, 4H), 2.04 – 1.76 (m, 2H).

Example 7

Preparation of 2-cyclopropyl-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)propanamide **Cpd-13**



Cpd-01c Cpd-13

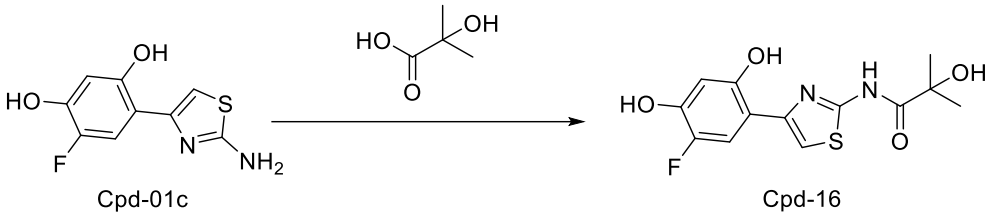
Cpd-01c (60 mg, 0.26 mmol), 2-cyclopropylpropanoic acid (181.62 mg, 1.59 mmol), BOP reagent (703.8 mg, 1.59 mmol) and *N,N*-diisopropylethylamine (274.2 mg, 2.1216 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 16 h. After the reaction was completed, the temperature was lowered to 45°C, and aqueous sodium hydroxide solution (8 mol/L, 1 mL) was added. The reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, dilute hydrochloric acid solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-13** (29.15 mg, white solid), with a yield of 34.09%.

MS m/z (ESI): 323.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 10.62 (s, 1H), 9.95 (s, 1H), 7.63 (d, *J* = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 1.92 (dt, *J* = 13.9, 6.9 Hz, 1H), 1.20 (d, *J* = 6.9 Hz, 3H), 0.99 – 0.90 (m, 1H), 0.55 – 0.47 (m, 1H), 0.44 – 0.36 (m, 2H), 0.19 – 0.11 (m, 1H).

Example 8

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-2-hydroxy-2-methylpropanamide **Cpd-16**



Cpd-01c Cpd-16

Cpd-01c (80 mg, 0.35 mmol), 2-hydroxy-2-methylpropanoic acid (220.9 mg, 2.12 mmol), BOP reagent (938.3 mg, 2.12 mmol) and *N,N*-diisopropylethylamine (137.1 mg, 1.06 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 16 h. After the reaction was completed, the temperature was lowered to 45°C, and aqueous sodium hydroxide solution (6 mol/L, 5 mL) was added. The reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-16** (20 mg), with a yield of 18%.

MS m/z (ESI): 313.1(M+1)

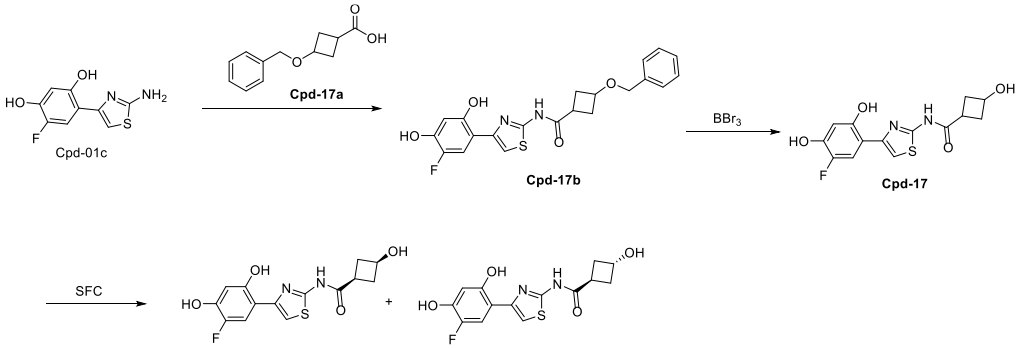
^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.76 (s, 1H), 10.90 (s, 1H), 9.95 (s, 1H), 7.62 (d, *J* = 12.6 Hz, 1H), 7.53 (s, 1H), 6.47 (d, *J* = 8.0 Hz, 1H), 5.81 (s, 1H), 1.39 (s, 6H).

Example 9

N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide **Cpd-17**

(1*s*,3*s*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide

(1*r*,3*r*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide



Step 1 Preparation of 3-(benzyloxy)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)cyclobutane-1-carboxamide **Cpd-17b**

4-(2-Aminothiazol-4-yl)-6-fluorobenzene-1,3-diol **Cpd-01c** (130 mg, 0.575 mmol) was dissolved in N,N-dimethylformamide solution (7 mL). To the system were added 3-(benzyloxy)cyclobutane-1-carboxylic acid **Cpd-17a** (711.03 mg, 3.45 mmol), BOP reagent (1.27 g, 2.87 mmol) and N,N-diisopropylethylamine (371 mg, 2.87 mmol). The system was heated to 55°C and stirred for 11 h. After the reaction was completed, water was added to quench the reaction. The mixture was extracted with ethyl acetate and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was combined with methanolic ammonia solution (4 mol/L, 5 mL), heated to 50°C and stirred for 1 h. After the reaction was completed, the system was concentrated to give a crude product. The crude product was subjected to silica gel column chromatography (petroleum ether : ethyl acetate = 100:55) to give 3-(benzyloxy)-N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazolyl-2-yl)cyclobutane-1-carboxamide **Cpd-17b** (215 mg) with a yield of 90%.

MS m/z (ESI): 415.1 (M+1)

Step 2 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide

3-(Benzyloxy)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)cyclobutane-1-carboxamide **Cpd-17b** (180 mg, 0.434 mmol) was dissolved in dichloromethane solution (8 mL). Boron tribromide (326 mg, 1.30 mmol) was added to the system under ice bath conditions. The ice bath was removed, and the mixture was warmed to 25°C and stirred for 1 h. After the reaction was completed, methanol was added to quench the reaction. The mixture was concentrated to yield a crude product. The crude product was purified by preparative high-performance liquid chromatography and lyophilized to afford racemic *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide **Cpd-17** (50 mg) with a yield of 35%.

MS m/z(ESI): 325.0 (M+1)

Step 3 Preparation of (1*s*,3*s*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide and (1*r*,3*r*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide

N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide **Cpd-17** (50 mg) was purified by chiral resolution (SFC 150, column: Daicel CHIRALCEL OZ, 250 mm × 30 mm I.D., 10μm; mobile phase 1: CO_2; mobile phase 2: MeOH [0.2% NH_3 (7M Solution in MeOH)]; gradient ratio: CO_2/MeOH [0.2% NH_3 (7M Solution in MeOH)]= 75/35, flow rate: 120 g/min). The fractions were lyophilized separately to afford the products **Cpd-17A** (30.07 mg, yield: 21%) and **Cpd-17B** (3.58 mg, yield: 2%).

Cpd-17A:

MS m/z(ESI): 325.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.12 (s, 1H), 10.71 (s, 1H), 10.00 (s, 1H), 7.61 (d, J = 12.7 Hz, 1H), 7.50 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 5.21 (s, 1H), 4.07 –3.96 (m, 1H), 2.75 (p, J = 9.8 Hz, 1H), 2.41 (dd, J = 13.0, 4.9 Hz, 2H), 2.03 (dd, J = 14.7, 6.2 Hz, 2H).

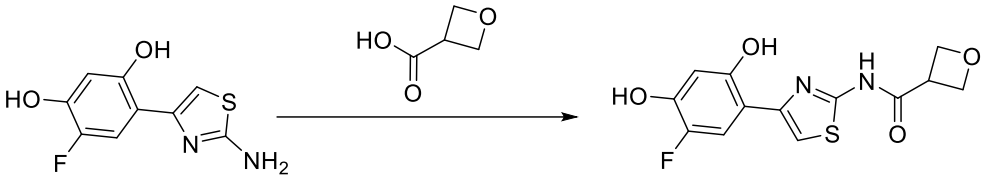
Cpd-17B:

MS m/z(ESI): 325.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.11 (s, 1H), 10.71 (s, 1H), 9.97 (s, 1H), 7.61 (d, J = 12.8 Hz, 1H), 7.50 (s, 1H), 6.49 (d, J = 7.9 Hz, 1H), 5.16 (d, J = 6.0 Hz, 1H), 4.30 (dd, J = 13.1, 6.7 Hz, 1H), 3.19 (t, J = 9.8 Hz, 1H), 2.44 – 2.39 (m, 2H), 2.15 – 2.07 (m, 2H).

Example 10

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)oxetane-3-carboxamide **Cpd-18**



Cpd-01c Cpd-18

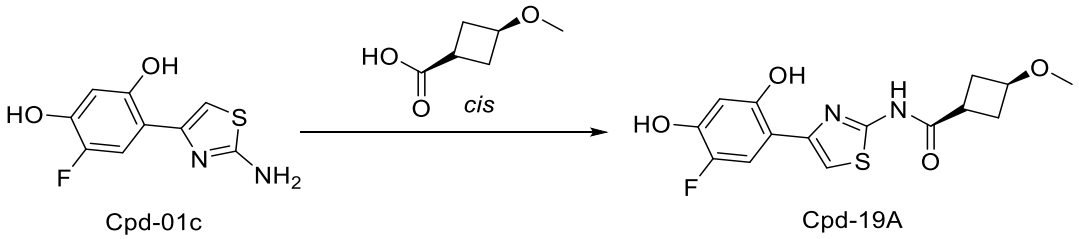
Cpd-01c (100 mg, 0.44 mmol), oxetane-3-carboxylic acid (270 mg, 2.64 mmol), BOP reagent (1168 mg, 2.64 mmol) and *N,N*-diisopropylethylamine (1135 mg, 8.80 mmol) were dissolved in *N,N*-dimethylformamide solution (10 mL). The mixture was stirred at 55°C for 6 h. After the reaction was completed, the temperature was lowered to 45°C, aqueous sodium hydroxide solution (6 mol/L, 5 mL) was added, and the reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-18** (21 mg), with a yield of 15%.

MS m/z (ESI): 311.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 10.56 (s, 1H), 9.93 (s, 1H), 7.62 (d, *J* = 12.8 Hz, 1H), 7.56 (s, 1H), 6.51 (d, *J* = 7.6 Hz, 1H), 4.77 – 4.66 (m, 4H), 4.09 (s, 1H).

Example 11

Preparation of cis-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-methoxycyclobutane-1-carboxamide **Cpd-19A**



Cpd-01c Cpd-19A

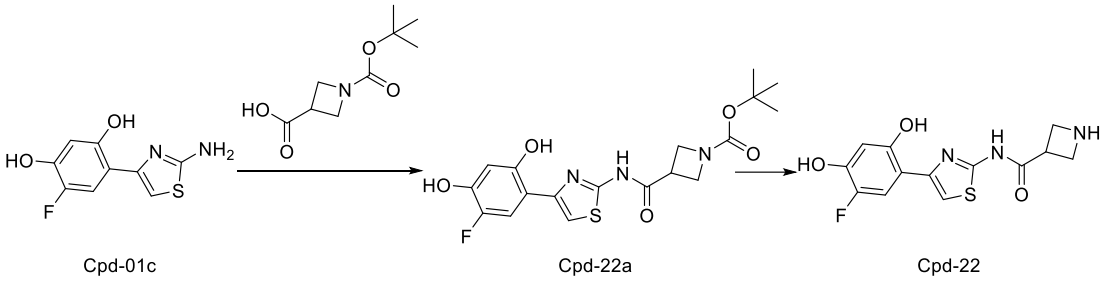
Cpd-01c (50 mg, 0.22 mmol), cis-3-methoxycyclobutane-1-carboxylic acid (172 mg, 1.32 mmol), BOP reagent (584 mg, 1.32 mmol) and *N,N*-diisopropylethylamine (568 mg, 4.40 mmol) were dissolved in *N,N*-dimethylformamide solution (5 mL). The mixture was stirred at 55°C for 6 h. After the reaction was completed, the temperature was lowered to 45°C, aqueous sodium hydroxide solution (6 mol/L, 2.5 mL) was added, and the reaction mixture was further stirred at 45°C for 5 h. Upon completion of the reaction, aqueous ammonium chloride solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by high performance liquid chromatography to afford the product **Cpd-19A** (15 mg), with a yield of 20%.

MS m/z (ESI): 339.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.19 (s, 1H), 10.62 (s, 1H), 9.95 (s, 1H), 7.62 (d, *J* = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.14 (s, 3H), 2.93 – 2.84 (m, 1H), 2.46 – 2.41 (m, 2H), 2.11 – 2.02 (m, 2H).

Example 12

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)azetidine-3-carboxamide **Cpd-22**



Step 1 Preparation of tert-butyl 3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)azetidine-1-carboxylate **Cpd-22a**

Cpd-01c (150 mg, 0.663 mmol) and 1-(tert-butoxycarbonyl)azetidine-3-carboxylic acid (801 mg, 3.98 mmol) were dissolved in N,N-dimethylformamide (7 mL). N,N-diisopropylethylamine (429 mg, 3.32 mmol) and BOP reagent (880 mg, 1.99 mmol) were then added to the system, which was stirred at 55°C for 11 h. After the reaction was completed, water was added to quench the reaction. The mixture was extracted with ethyl acetate and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was mixed with methanolic ammonia solution (4 mol/L, 5 mL), heated to 50°C and stirred for 1 h. After the reaction was completed, the system was concentrated to give crude **Cpd-22a** (260 mg, yellow solid), with a yield of 76.6%.

MS m/z (ESI): 410.1 (M+1)

Step 2 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)azetidine-3-carboxamide **Cpd-22**

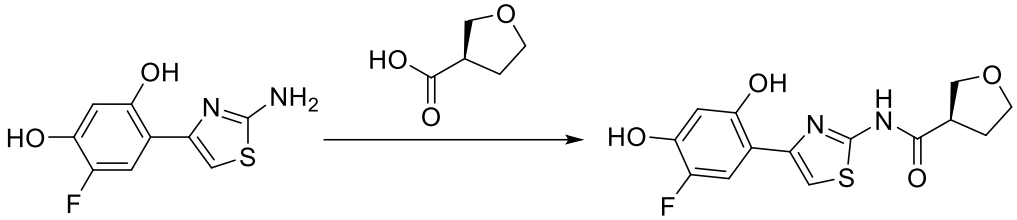
Cpd-22a (260 mg, 0.635 mmol) was dissolved in dichloromethane solution (7 mL). Hydrochloric acid/1,4-dioxane solvent (4 mmol/L, 6.35 mmol) was added to the system under ice bath conditions. The ice bath was removed, and the mixture was warmed to 25°C and stirred for 1 h. After the reaction was completed, the system was concentrated to afford a crude product. The crude product was purified by preparative high performance liquid chromatography (Waters MS-triggered Prep-LC with SQD2 detector, column: Xbridge 5u C18 150 *19 mm; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 15-min gradient, gradient ratio: acetonitrile phase 12%-100%, flow rate: 20 mL/min), and lyophilized to give the product **Cpd-22** (11.9 mg) with a yield of 6%.

MS m/z(ESI): 310.0 (M+1).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.60 (d, J = 12.8Hz, 1H), 7.51 (s, 1H), 6.51 (d, J = 8.0Hz, 1H), 4.01 - 3.95 (m, 2H), 3.89 (t, J = 8.9Hz, 2H), 3.79 (dd, J = 16.5, 8.0Hz, 1H)

Example 13

Preparation of (*R*)-*N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)tetrahydrofuran-3-carboxamide **Cpd-36A**



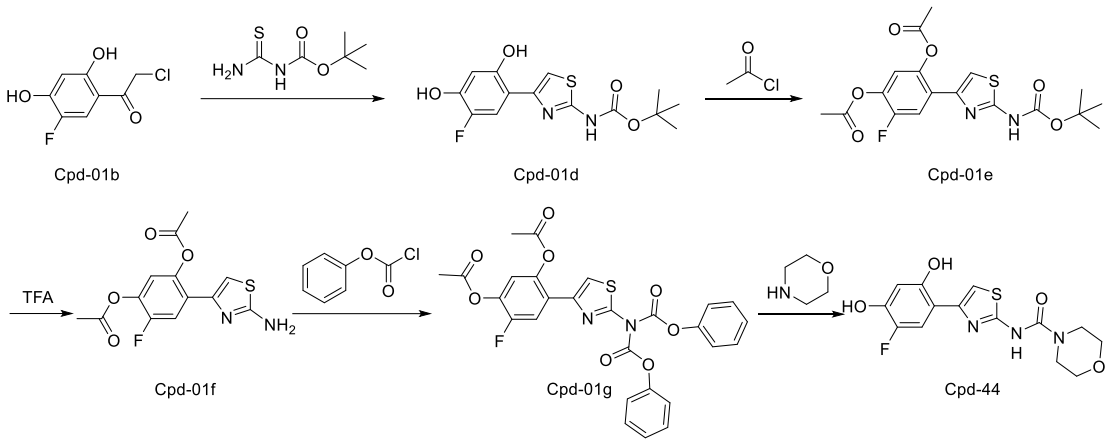
Cpd-01c (60 mg, 0.26 mmol) and (*R*)-tetrahydrofuran-3-carboxylic acid (184.76 mg, 1.59 mmol) were dissolved in N,N-dimethylformamide (2 mL). *N,N*-diisopropylethylamine (102.63 mg, 0.79 mmol) and BOP reagent (703.77 mg, 1.59 mmol) were added to the mixture, and the mixture was stirred at 55°C for 16 h. After the reaction was completed, water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was mixed with methanolic ammonia solution (4 mol/L, 5 mL), and stirred at 25°C for 1 h. After the reaction was completed, methanol was removed by rotary evaporation. The mixture was extracted with ethyl acetate and water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was purified by preparative high performance liquid chromatography (Waters MS-triggered Prep-LC with SQD2 detector, column: Xbridge 5u C18 150 *19 mm; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 15-min gradient, gradient ratio: acetonitrile phase 42%-52%, flow rate: 20 mL/min), and lyophilized to give the product **Cpd-36A** (20.92 mg) with a yield of 23%.

MS m/z(ESI): 325.0 (M+1).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 10.61 (s, 1H), 9.96 (s, 1H), 7.63 (d, *J* = 12.8 Hz, 1H), 7.54 (s, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 3.93 (t, *J* = 8.3 Hz, 1H), 3.83 – 3.68 (m, 3H), 3.32 – 3.26 (m, 1H), 2.19 – 2.05 (m, 2H).

Example 14

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)morpholine-4-carboxamide **Cpd-44**



Step 1 Preparation of tert-butyl (4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamate **Cpd-01d**

Crude **Cpd-01b** (22 g), N-Boc thiourea (7.5 g, 0.042 mol) and pyridine (5.5 g, 0.070 mol) were dissolved in dioxane solution (100 mL). The reaction mixture was stirred at 90°C for 6 h. After completion of the reaction, the mixture was cooled to room temperature and diluted with ethyl acetate. The organic phase was washed with citric acid solution and saturated brine, then dried and concentrated to afford a crude product. The crude product was triturated with dichloromethane and diethyl ether to give **Cpd-01d** (3.2 g, white solid) with a yield of 22.5% (based on thiourea).

MS m/z (ESI): 327.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.66 (s, 1H), 10.80 (s, 1H), 9.94 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.47 (s, 1H), 6.46 (d, J = 7.9 Hz, 1H), 1.50 (s, 9H).

Step 2 Preparation of 4-(2-((tert-butoxycarbonyl)amino)thiazol-4-yl)-6-fluoro-1,3-phenylene diacetate **Cpd-01e**

Cpd-01d (3.2 g, 10 mmol) was dissolved in 30 mL of tetrahydrofuran, followed by addition of triethylamine (4.04 g, 40 mmol). The mixture was cooled to 0°C, and acetyl chloride (1.72 g, 22 mmol) was added dropwise slowly. The reaction was stirred at 0°C for 2 h. Upon completion of the reaction, the mixture was partitioned between water and ethyl acetate. The organic phase was dried and concentrated to afford crude **Cpd-01e**, which was used directly in the next step (4.10 g, crude yield: 100%).

MS m/z (ESI): 205.1(M+1)

Step 3 Preparation of 4-(2-aminothiazol-4-yl)-6-fluoro-1,3-phenylene diacetate **Cpd-01f**

Cpd-01e (4.10 g, 10 mmol) was dissolved in 20 mL of dichloromethane, and 10 mL of trifluoroacetic acid was added. The reaction mixture was stirred at room temperature for 4 h. After the reaction was completed, the reaction mixture was concentrated and then partitioned between water and ethyl acetate. The organic phase was washed with saturated sodium bicarbonate solution, dried and concentrated to give the product **Cpd-01f** (2.5 g) with a yield of 80%.

MS m/z (ESI): 311.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.79 (d, *J* = 11.8 Hz, 1H), 7.22 (d, *J* = 7.0 Hz, 1H), 7.10 (s, 2H), 6.97 (s, 1H), 2.34 (d, *J* = 5.5 Hz, 6H).

Step 4 Preparation of 4-(2-(bis(phenoxycarbonyl)amino)thiazol-4-yl)-6-fluoro-1,3-phenylene diacetate **Cpd-01g**

Cpd-01f (150 mg, 0.48 mmol) and N,N-diisopropylethylamine (187 mg, 1.45 mmol) were dissolved in dichloromethane (5 mL), and phenyl chloroformate (150 mg, 0.96 mmol) was added. The mixture was stirred at 25°C for 1 h. The reaction was monitored by TLC until completion. The resulting mixture was concentrated to afford crude **Cpd-01g** (200 mg, brown solid).

MS m/z (ESI): 551.2(M+1)

Step 5 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)morpholine-4-carboxamide **Cpd-44**

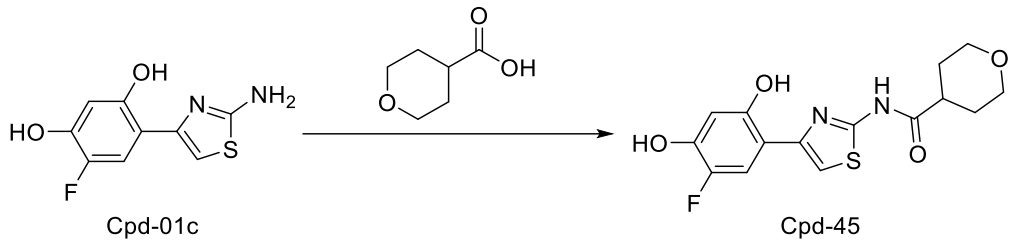
Crude **Cpd-01g** (200 mg) and morpholine (200 mg, 2.29 mmol) were dissolved in pyridine solution (5 mL). The reaction mixture was stirred at 90°C for 2 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was dissolved in methanolic ammonia solution, and the reaction mixture was stirred at 25°C for 1 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford the product **Cpd-44** (50 mg), with a yield of 31% over two steps.

MS m/z (ESI): 340.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.99 (d, 2H), 9.92 (s, 1H), 7.60 (d, *J* = 12.7 Hz, 1H), 7.39 (s, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 3.66 – 3.58 (m, 4H), 3.55 – 3.47 (m, 4H).

Example 15

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)tetrahydro-2*H*-pyran-4-carboxamide **Cpd-45**



Cpd-01c Cpd-45

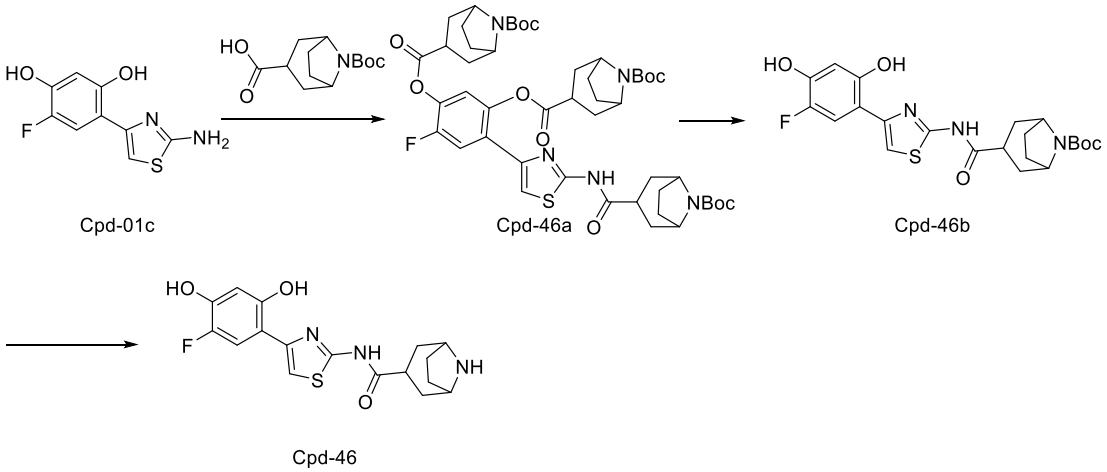
Cpd-01c (80 mg, 0.3536 mmol) and tetrahydro-2*H*-pyran-4-carboxylic acid (276.11 mg, 2.1216 mmol) were dissolved in N,N-dimethylformamide (2 mL). *N,N*-diisopropylethylamine (136.84 mg, 1.0608 mmol) and BOP reagent (938.36 mg, 2.1216 mmol) were added to the system, which was then stirred at 55°C for 16 h. After the reaction was completed, water was added to quench the reaction. The mixture was extracted with ethyl acetate, and the organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was mixed with methanolic ammonia solution (4 mol/L, 5 mL), and stirred at 25°C for 1 h. After the reaction was completed, methanol was removed by rotary evaporation. The mixture was extracted with ethyl acetate and water. The organic phase was washed with saturated brine, dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was purified by preparative high performance liquid chromatography (Waters MS-triggered Prep-LC with SQD2 detector, column: Xbridge 5u C18 150 *19 mm; mobile phase 1: water (containing 0.1% FA); mobile phase 2: acetonitrile; 15-min gradient, gradient ratio: acetonitrile phase 42%-52%, flow rate: 20 mL/min), and lyophilized to give the product **Cpd-45** (37.57 mg) with a yield of 30%.

MS m/z(ESI): 339.0 (M+1).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.22 (s, 1H), 10.67 (s, 1H), 9.96 (s, 1H), 7.63 (d, *J* = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, *J* = 7.9 Hz, 1H), 3.95 – 3.87 (m, 2H), 3.35 (td, *J* = 11.5, 2.1 Hz, 2H), 2.82 – 2.71 (m, 1H), 1.80 – 1.60 (m, 4H).

Example 16

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide **Cpd-46**



Cpd-01c Cpd-46a Cpd-46b

Cpd-46

Step 1 Preparation of 4-(2-(8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-formamido)thiazol-4-yl)-6-fluoro-1,3-phenylene bis(8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylate) **Cpd-46a**

Cpd-01c (100 mg, 0.44 mmol), *N*,*N*-diisopropylethylamine (285 mg, 2.21 mmol), 8-(tert-butoxycarbonyl)-8-azabicyclo[3.2.1]octane-3-carboxylic acid (277 mg, 2.65 mmol) and BOP reagent (977 mg, 2.21 mmol) were dissolved in N,N-dimethylformamide (5 mL). The mixture was stirred at room temperature for 16 h. After the reaction was completed, water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to afford crude **Cpd-46a** (500 mg, yellow oil) with a yield of 96.47%.

MS m/z (ESI): 938.3 (M+1)

Step 2 Preparation of tert-butyl 3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)-8-azabicyclo[3.2.1]octane-8-carboxylate **Cpd-46b**

Cpd-46a (450 mg, 0.47 mmol) was dissolved in methanol solution (3 mL), and then sodium hydroxide solution (12 M, 2 mL) was added and stirred at room temperature for 4 h. After the reaction completed, the solvent was removed by concentration. The residue was extracted with ethyl acetate, and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to afford crude Cpd-46b (200 mg, yellow oil) with a yield of 80.95%.

MS m/z (ESI): 464.2(M+1)

Step 3 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-8-azabicyclo[3.2.1]octane-3-carboxamide **Cpd-46**

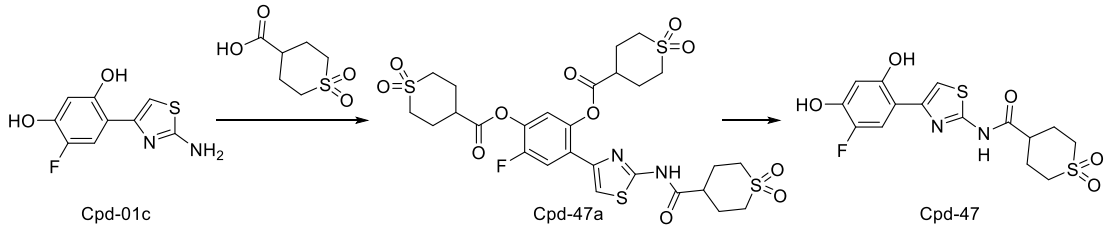
Cpd-46b (200 mg, 0.43 mmol) was dissolved in dichloromethane (3 mL), and then trifluoroacetic acid (98 mg, 0.86 mmol) was added. The reaction mixture was stirred at 20°C for 2 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% 0.1FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford the product **Cpd-46** (150 mg), with a yield of 86.0%.

MS m/z (ESI): 364.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.69 (s, 2H), 7.61 (d, *J* = 12.8 Hz, 1H), 7.51 (s, 1H), 6.52 (d, *J* = 8.0 Hz, 1H), 3.85 (s, 2H), 3.08 – 2.93 (m, 1H), 1.88 (dd, *J* = 28.1, 16.4 Hz, 8H).

Example 17

N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide



Step 1 Preparation of 4-(2-(tetrahydro-2*H*-thiopyran-4-carboxamido 1,1-dioxide)thiazol-4-yl)-6-fluoro-1,3-phenylene bis(tetrahydro-2*H*-thiopyran-4-carboxylate 1,1-dioxide) **Cpd-47a**

Cpd-01c (60 mg, 0.26 mmol) and tetrahydro-2*H*-thiopyran-4-carboxylic acid 1,1-dioxide (189 mg, 1.06 mmol) were dissolved in *N,N*-dimethylformamide (3 mL). Then, BOP reagent (586 mg, 1.32 mmol) and *N,N*-diisopropylethylamine (342 mg, 2.65 mmol) were added. The mixture was stirred at room temperature for 16 h. After the reaction was completed, water was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to afford crude **Cpd-47a** (110 mg, black oil) with a yield of 46.95%.

MS m/z (ESI): 707.0 (M+1)

Step 2 Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)tetrahydro-2*H*-thiopyran-4-carboxamide 1,1-dioxide **Cpd-47**

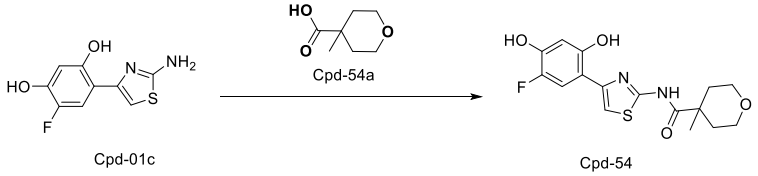
Cpd-47a (120 mg, 0.16 mmol) was dissolved in methanol/water solution (1 mL/1 mL), followed by the addition of sodium hydroxide (13 mg, 0.33 mmol). The reaction mixture was stirred at 20°C for 2 h. After the reaction was completed, the reaction mixture was concentrated to give a crude product. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% 0.1FA); mobile phase 2: acetonitrile; 18 min gradient, gradient ratio: acetonitrile phase 5%-100%, flow rate: 30 mL/min). The purified fraction was lyophilized to afford **Cpd-47** (51.47 mg), with a yield of 78.15%.

MS m/z (ESI): 387.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 10.66 (s, 1H), 9.96 (s, 1H), 7.63 (d, *J* = 12.8 Hz, 1H), 7.55 (s, 1H), 6.51 (d, *J* = 8.0 Hz, 1H), 3.28 –3.10 (m, 4H), 2.86 (ddd, *J* = 10.8, 7.6, 3.5 Hz, 1H), 2.25 (d, *J* = 11.2 Hz, 2H), 2.11 (dd, *J* = 19.2, 8.0 Hz, 2H).

Example 18

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-4-methyltetrahydro-2*H*-pyran-4-carboxamide **Cpd-54**



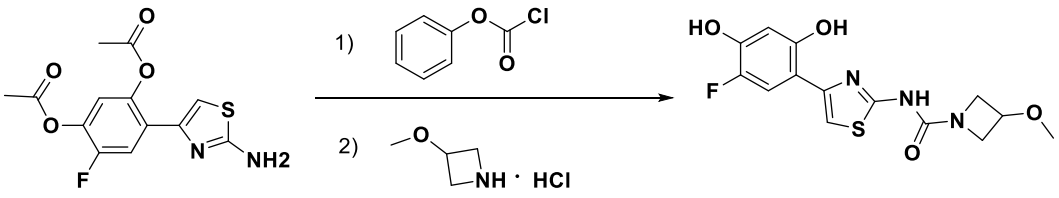
4-(2-Aminothiazol-4-yl)-6-fluorobenzene-1,3-diol **Cpd-01c** (1 g, 4.4 mmol), 4-methyltetrahydro-2*H*-pyran-4-carboxylic acid **Cpd-54a** (3.91 g, 26.4 mmol), benzotriazol-1-yloxytri(dimethylamino)phosphonium hexafluorophosphate (11.68 g, 26.4 mmol) and N,N-diisopropylethylamine (3.42 g, 26.4 mmol) were dissolved in anhydrous N,N-dimethylformamide (20 mL). The mixture was stirred at 55°C for 16 h. After the reaction was completed, saturated aqueous ammonium chloride solution was added to quench the reaction. The reaction mixture was extracted with ethyl acetate. The organic layer was dried over anhydrous sodium sulfate and concentrated. The obtained crude compound was added to ammonia-methanol solution (10 mL, 4M), and the reaction mixture was allowed to react at room temperature for 2 h. Upon completion of the reaction, the reaction mixture was dried by rotary evaporation. Saturated aqueous ammonium chloride solution was added, followed by extraction with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (ethyl acetate/petroleum ether = 40%) to give the product *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-4-methyltetrahydro-2*H*-pyran-4-carboxamide **Cpd-54** (870 mg) with a yield of 56%.

MS m/z (ESI): 353.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.88 (s, 1H), 10.74 (s, 1H), 9.95 (s, 1H), 7.66 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 3.74 –3.64 (m, 2H), 3.44 (t, J = 9.0 Hz, 2H), 2.12 (d, J = 14.1 Hz, 2H), 1.59 – 1.50 (m, 2H), 1.30 (s, 3H).

Example 19

Preparation of *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-methoxyazetidine-1-carboxamide **Cpd-107**



Cpd-01f Cpd-107a **Cpd-107**

Under nitrogen protection, pyridine (61 mg, 0.774 mmol) and phenyl chloroformate (61 mg, 0.387 mmol) were added to a solution of 4-(2-aminothiazol-4-yl)-6-fluoro-1,3-phenylene diacetate **Cpd-01f** (60 mg, 0.193 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred at room temperature for 1 h. After the reaction was completed, the reaction mixture was dried by rotary evaporation. The residue was triturated twice with petroleum ether, and the collected solid was dried by rotary evaporation to afford a crude product. The crude product was then dissolved in pyridine (0.5 mL), followed by addition of 3-methoxyazetidine hydrochloride **Cpd-107a** (60 mg, 0.484 mmol). The reaction mixture was stirred at 90°C for 1.5 h. Upon completion of the reaction, the reaction mixture was dried by rotary evaporation to give a crude product. The crude

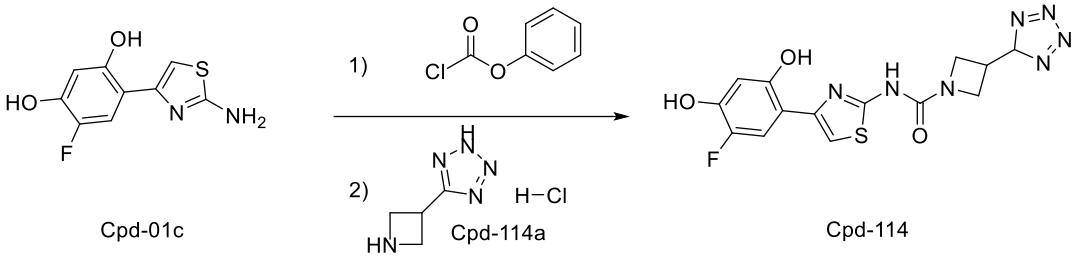
product was then dissolved in a solution of ammonia in methanol (4 mol/L, 1 mL). The reaction mixture was stirred at 50°C for 1 h, dried by rotary evaporation, the resulting crude product was purified by preparative high-performance liquid chromatography to give *N*-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-methoxyazetidine-1-carboxamide **Cpd-107** (30.54 mg) with a yield of 46%.

MS m/z(ESI): 340.1 (M+1).

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 10.93 (s, 1H), 9.91 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.22 (s, 3H), 3.83 (d, J = 6.4 Hz, 2H), 3.22 (s, 3H).

Example 20

N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-(2*H*-tetrazol-5-yl)azetidine-1-carboxamide



Cpd-01c (3 g, 13.26 mmol) was dissolved in dichloromethane (20 mL), pyridine (4.19 g, 53 mmol) was added, and phenyl chloroformate (10.38 g, 66.3 mmol) was slowly added dropwise. The mixture was stirred at 25°C for 1 h. After the reaction was complete, petroleum ether was added dropwise to the solution until no more precipitate was formed. The solution was then filtered, and the residue was the crude product (9 g). The crude product (4.2 g) was dissolved in pyridine (20 mL), and 5-(azetidin-3-yl)-2H-tetrazole hydrochloride **Cpd-114a** (2.14 g, 13.3 mmol) was added. The mixture was stirred at 90°C for 2 h, and the mixture was dried by rotary evaporation after the reaction was completed. The crude product was purified by preparative high-performance liquid chromatography (Waters MS-triggered Prep-LC with QDA detector, column: WELCH Xtimate C18 21.2*250mm 10um; mobile phase 1: water (containing 0.1% NH_4HCO_3); mobile phase 2: acetonitrile; 10 min gradient, gradient ratio: acetonitrile phase 10%-35%, flow rate: 15 mL/min) to afford the compound N-(4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)-3-(2H-tetrazol-5-yl)azetidine-1-carboxamide **Cpd-114** (364.21 mg), with a yield of 15.6%.

MS m/z (ESI): 378.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.98 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 7.9 Hz, 1H), 4.39 (t, J = 7.8 Hz, 2H), 4.22 – 4.09 (m, 2H), 4.02 (dt, J = 8.8, 7.5 Hz, 1H).

Example 21

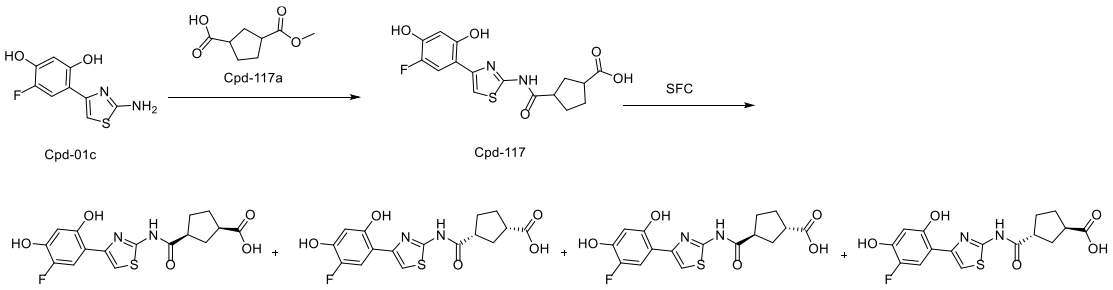
3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid **Cpd-117**

(1R,3S)-3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid

(1S,3R)-3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid

(1S,3S)-3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid

(1R,3R)-3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid



Step 1 Preparation of 3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid **Cpd-117**

Cpd-01c (1.50 g, 6.63 mmol) was dissolved in N,N-dimethylformamide solution (40 mL), 3-(methoxycarbonyl)cyclopentane-1-carboxylic acid **Cpd-117a** (5.13 g, 29.84 mmol), BOP reagent (13.19 g, 29.84 mmol) and N,N-diisopropylethylamine (7.70 g, 59.67 mmol) were added. The reaction mixture was stirred at 55°C for 16 h. After the reaction was completed, the reaction mixture was poured into water (40 mL), and the mixture was extracted with ethyl acetate (20 mL × 2). The organic phase was concentrated to dryness to afford a crude brown oil. The crude product was dissolved in methanol (20 mL), and aqueous sodium hydroxide solution (4 M, 20 mL) was added. The reaction mixture was stirred at 25°C for 1 h. After the reaction was completed, the reaction mixture was concentrated to afford a crude product. The crude product was purified by silica gel column chromatography (petroleum ether : ethyl acetate = 2:1) to give the product 3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid **Cpd-117** (1.3 g, white solid) with a yield of 54%.

MS m/z (ESI): 367.0(M+1)

Step 2

The compound 3-((4-(5-fluoro-2,4-dihydroxyphenyl)thiazol-2-yl)carbamoyl)cyclopentane-1-carboxylic acid (1.3 g, 3.55 mmol) was purified by SFC (Apparatus: SFC 150, Column: Daicel CHIRALCEL AD, 250 mm × 30 mm I.D., 10μm, Mobile phase: CO_2/MeOH [0.2%NH_3(7M Solution in MeOH)] = 65/35, Flow rate: 120 g/min, Wavelength: UV 214 nm, Temperature: 35 $^{°C}$) to afford **Cpd-117A, Cpd-117B, Cpd-117C and Cpd-117D**. The characterization data are shown below.

Cpd-117A (330 mg), yield: 25%

MS m/z (ESI): 367.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.71 (s, 2H), 7.62 (d, *J* = 12.7 Hz, 1H), 7.51 (s, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 3.05 – 2.92 (m, 1H), 2.82 – 2.69 (m, 1H), 2.24 – 2.12 (m, 1H), 2.04 – 1.76 (m, 5H).

Cpd-117B (310 mg), yield: 24%

MS m/z (ESI): 367.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.68 (s, 2H), 7.62 (d, *J* = 12.7 Hz, 1H), 7.51 (s, 1H), 6.50 (d, *J* = 8.0 Hz, 1H), 3.04 – 2.93 (m, 1H), 2.84 – 2.70 (m, 1H), 2.23 – 2.11 (m, 1H), 2.01 – 1.80 (m, 5H).

Cpd-117C (33 mg), yield: 2.5%

MS m/z (ESI): 367.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 7.7 Hz, 1H), 3.13 – 3.02 (m, 1H), 2.91 –2.82 (m, 1H), 2.13 – 1.94 (m, 4H), 1.83 – 1.71 (m, 2H).

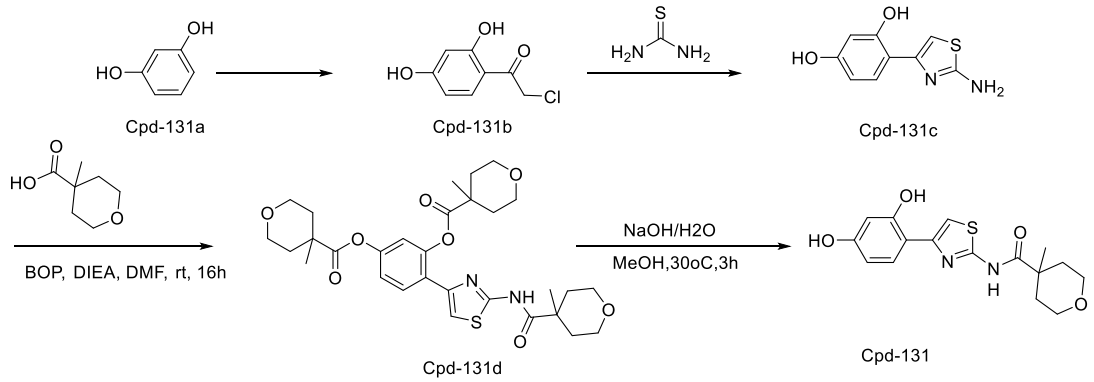
Cpd-117D (31 mg), yield: 2.4%

MS m/z (ESI): 367.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 12.13 (s, 1H), 10.68 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H),3.15 – 3.00 (m, 1H), 2.92 – 2.78 (m, 1H), 2.16 – 1.93 (m, 4H), 1.85 – 1.68 (m, 2H).

Example 22

Preparation of N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-4-methyltetrahydro-2*H*-pyran-4-carboxamide **Cpd-131**



Step 1 Preparation of 2-chloro-1-(2,4-dihydroxyphenyl)ethan-1-one

Resorcinol **Cpd-131a** (35 g, 0.31 mol) was dissolved in 300 mL of dioxane hydrochloride, followed by the addition of zinc chloride (21.7 g, 0.17 mol). Bromoacetonitrile (37.0 g, 0.35 mol) was then added slowly at 0°C, and the reaction mixture was stirred at 20°C for 16 h. The reaction was monitored until the starting material was completely consumed, 100 ml of water was then

added, and the reaction mixture was heated to 80°C and stirred for 3 h. After completion of the reaction, the system was cooled to room temperature and extracted with ethyl acetate. The organic phase was washed once with saturated sodium bicarbonate solution and twice with saturated brine. The organic phase was concentrated and further purified by trituration with ethyl acetate to afford the product 2-chloro-1-(2,4-dihydroxyphenyl)ethan-1-one **Cpd-131b** (48 g) with a yield of 83%.

MS m/z (ESI): 187.0 (M+1)

Step 2 Preparation of 4-(2-aminothiazol-4-yl)benzene-1,3-diol

2-Chloro-1-(2,4-dihydroxyphenyl)ethan-1-one **Cpd-131b** (10 g, 0.053 mol) was dissolved in 100 mL of dioxane, and then thiourea (4.13 g, 0.053 mol) was added. The mixture was stirred at 80°C for 3 h. After the reaction was completed, the mixture was filtered to collect the filter cake. The filter cake was then washed with saturated sodium bicarbonate solution, filtered and dried to give 4-(2-aminothiazol-4-yl)benzene-1,3-diol **Cpd-131c** (9 g) with a yield of 81%.

MS m/z (ESI): 209.0 (M+1)

Step 3 Preparation of 4-(2-(4-methyltetrahydro-2*H*-pyran-4-carboxamido)thiazol-4-yl)-1,3-phenylene bis(4-methyltetrahydro-2*H*-pyran-4-carboxylate)

4-(2-Aminothiazol-4-yl)benzene-1,3-diol **Cpd-131c** (100 mg, 0.48 mmol), 4-methyltetrahydro-2*H*-pyran-4-carboxylic acid (346 mg, 2.4 mmol), BOP reagent (1.06 g, 2.4 mmol) and N,N-diisopropylethylamine (619 mg, 4.8 mmol) were dissolved in N,N-dimethylformamide solution (5 mL). The mixture was stirred at 55°C for 16 h. After the reaction completed, the reaction mixture was poured into water and extracted twice with ethyl acetate (30 mL). The organic layer was washed with saturated brine, dried over anhydrous sodium sulfate, and concentrated to dryness to afford crude 4-(2-(4-methyltetrahydro-2*H*-pyran-4-carboxamido)thiazol-4-yl)-1,3-phenylene bis(4-methyltetrahydro-2*H*-pyran-4-carboxylate) **Cpd-131d** (110 mg), which was used directly in the next step.

Step 4 Preparation of N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-4-methyltetrahydro-2*H*-pyran-4-carboxamide **Cpd-131**

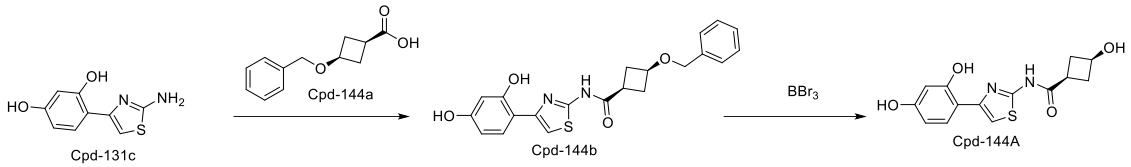
To a solution of crude 4-(2-(4-methyltetrahydro-2*H*-pyran-4-carboxamido)thiazol-4-yl)-1,3-phenylene bis(4-methyltetrahydro-2*H*-pyran-4-carboxylate) **Cpd-131d** (110 mg) in methanol was added aqueous sodium hydroxide solution (8 mol/L, 2 mL). The reaction mixture was stirred continuously at 50°C for 1 h. Upon completion of the reaction, dilute hydrochloric acid solution was added, and the mixture was extracted with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated. The crude product was purified by preparative high performance liquid chromatography to give the product N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-4-methyltetrahydro-2*H*-pyran-4-carboxamide **Cpd-131** (43 mg), with an overall yield of 26% over two steps.

MS m/z (ESI): 335.0(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.88 (s, 1H), 10.95 (s, 1H), 9.47 (s, 1H), 7.68(d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 6.31-6.28 (m, 2H), 3.70-3.66 (m, 2H), 3.46-3.41(m, 2H), 2.17-2.06 (m, 2H), 1.55-1.51 (m, 2H), 1.30 (s, 3H).

Example 23

Preparation of (1s,3s)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide **Cpd-144A**



Step 1 Preparation of (1s,3s)-3-(benzyloxy)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)cyclobutane-1-carboxamide **Cpd-144b**

4-(2-Aminothiazol-4-yl)benzene-1,3-diol Cpd-131c (130 mg, 0.625 mmol) was dissolved in N,N-dimethylformamide solution (10 mL), and (1s,3s)-3-(benzoyloxy)cyclobutane-1-carboxylic acid **Cpd-144a** (644.5 mg, 3.125 mmol), BOP reagent (1.10 g, 2.5 mmol) and N,N-diisopropylethylamine (323 mg, 2.5 mmol) were added to the system. The system was heated to 55°C and stirred overnight. After the reaction was completed, water was added to quench the reaction. The mixture was extracted with ethyl acetate and washed with saturated brine, the organic phase was dried over anhydrous sodium sulfate and concentrated to give a crude product. The crude product was combined with methanolic ammonia solution (4 mol/L, 5 mL), heated to 50°C and stirred for 1 h. Upon completion of the reaction, the system was concentrated to give a crude product, which was further purified by trituration with ethyl acetate to yield (1s,3s)-3-(benzyloxy)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)cyclobutane-1-carboxamide **Cpd-144b** (390 mg) with a yield of 86%.

MS m/z (ESI): 397.0 (M+1)

Step 2 Preparation of (1s,3s)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclobutane-1-carboxamide **Cpd-144A**

Cpd-144b (390 mg, 0.0984 mmol) was dissolved in 2 mL of dichloromethane, and then 1 mL of boron tribromide was added. The reaction mixture was stirred at 20°C for 1 h. After the reaction was completed, methanol was added dropwise to quench the reaction, the reaction mixture was concentrated, and then purified by preparative silica gel plate (petroleum ether/ethyl acetate = 1/1) to afford the product **Cpd-144A** (250 mg) with a yield of 83.4%.

MS m/z (ESI): 307.0 (M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.15 (s, 1H), 10.85 (s, 1H), 9.48 (s, 1H), 7.65 (d, *J* = 8.3 Hz, 1H), 7.41 (s, 1H), 6.30 (dt, *J* = 8.3, 2.3 Hz, 2H), 5.21 (d, *J* = 7.0 Hz, 1H), 4.02 (dd, *J* = 15.1,

8.1 Hz, 1H), 2.75 (td, *J* = 9.7, 4.9 Hz, 1H), 2.40 (ddd, *J* = 15.2, 7.4, 2.8 Hz, 2H), 2.11 – 2.00 (m, 2H)

Example 24

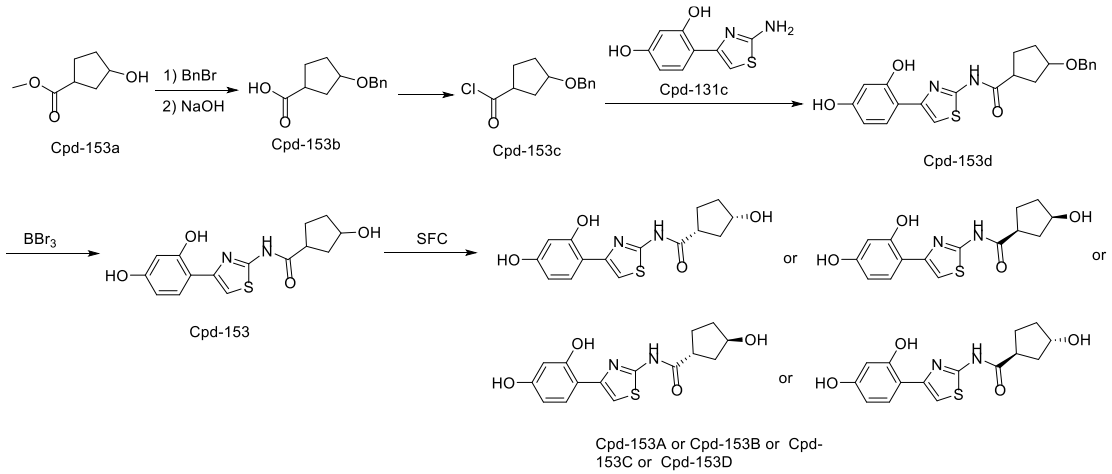
N-(4-(2,4-Dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide **Cpd-153**

(1R,3S)- *N*-(4-(2,4-Dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide

(1S,3R)- *N*-(4-(2,4-Dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide

(1R,3R)- *N*-(4-(2,4-Dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide

(1S,3S)- *N*-(4-(2,4-Dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide



Step 1 Preparation of 3-(benzyloxy)cyclopentane-1-carboxylic acid **Cpd-153b**

Methyl 3-hydroxycyclopentane-1-carboxylate Cpd-153a (1 g, 6.9 mmol) and benzyl bromide (1.54 g, 8.97 mmol) were dissolved in anhydrous tetrahydrofuran solution (10 mL). Sodium hydride (330 mg, 13.8 mmol) was added at 0°C, and the reaction mixture was stirred at 0°C for 2 h. After the reaction was completed, an aqueous solution was added to quench the reaction. The reaction mixture was extracted with ethyl acetate, and the organic phase was dried over anhydrous sodium sulfate and concentrated. The crude compound was dissolved in methanol solution (5 mL), and sodium hydroxide (276 mg, 6.9 mmol) was added. The reaction mixture was allowed to react at 55°C for 1 h. Upon completion of the reaction, the reaction mixture was dried by rotary evaporation. Concentrated hydrochloric acid was added to adjust the pH to 2–3, followed by extraction with ethyl acetate. The organic phase was dried over anhydrous sodium sulfate and concentrated to afford crude 3-(benzyloxy)cyclopentane-1-carboxylic acid **Cpd-153b** (1.45 g) with a yield of 95%.

MS m/z (ESI): 221.2(M+1)

Step 2 Preparation of 3-(benzyloxy)cyclopentane-1-carbonyl chloride **Cpd-153c**

3-(Benzyloxy)cyclopentane-1-carboxylic acid **Cpd-153b** (1.45 g, 6.9 mmol) was dissolved in anhydrous dichloromethane solution (20 mL). N,N-Dimethylformamide (96 mg, 1.38 mmol) was added, and oxalyl chloride (1.25 g, 9.88 mmol) was added dropwise slowly at 0°C. The mixture was stirred at room temperature for 1 h. After the reaction was completed, the mixture was

concentrated to give crude 3-(benzyloxy)cyclopentane-1-carbonyl chloride **Cpd-153c** (1.32 g) with a yield of 84%.

Step 3 Preparation of 3-(benzyloxy)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)cyclopentane-1-carboxamide **Cpd-153d**

4-(2-Aminothiazol-4-yl)benzene-1,3-diol Cpd-131c (191 mg, 0.92 mmol) was dissolved in dichloromethane solution (20 mL), and triethylamine (750 mg, 7.36 mmol) was added. A solution of 3-(benzyloxy)cyclopentane-1-carbonyl chloride **Cpd-153c** (1.64 g, 5.5 mmol) in anhydrous dichloromethane solution (2 mL) was then added slowly. The reaction mixture was stirred at room temperature for 1 h, followed by the addition of sodium hydroxide (110 mg, 2.76 mmol). The reaction mixture was stirred at 55°C for 1 h. Upon completion of the reaction, the reaction mixture was concentrated and purified by silica gel column chromatography (petroleum ether/ethyl acetate = 10/1) to afford 3-(benzyloxy)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)cyclopentane-1-carboxamide **Cpd-153d** (80 mg) with a yield of 21%.

MS m/z (ESI): 411.1(M+1)

Step 4 Preparation of N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide **Cpd-153**

3-(Benzyloxy)-N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)cyclopentane-1-carboxamide **Cpd-153d** (80 mg, 0.19 mmol) was dissolved in dichloromethane solution. Boron tribromide (3 drops) was added slowly. The reaction mixture was allowed to react at room temperature for 1 h. Crude N-(4-(2,4-dihydroxyphenyl)thiazol-2-yl)-3-hydroxycyclopentane-1-carboxamide **Cpd-153** (30 mg, 0.09 mmol) was obtained after purification via silica gel column chromatography (petroleum ether/ethyl acetate = 10/1).

Step 5 Chiral resolution by SFC

After purification by SFC (Apparatus: SFC 150, Column: Daicel CHIRALCEL OZ, 250mm ×, 30mm ID, 10μm, Mobile phase: CO_2/EtOH [0.2%NH3(7M Solution in MeOH)] = 80/20, Flow rate: 120 g/min, Wavelength: UV 214 nm, Temperature: 35°C), lyophilization was conducted to afford **Cpd-153A** (1.02 mg, t_R= 1.943 min, yield: 1.6%).

MS m/z (ESI): 321.1(M+1)

^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.21 (s, 1H), 10.90 (s, 1H), 9.48 (s, 1H), 7.65 (d, J = 8.4 Hz, 1H), 7.40 (s, 1H), 6.31 (s, 2H), 4.57 (d, J = 4.0 Hz, 1H), 4.24 (d, J= 4.0 Hz, 1H), 3.17 (dt, J = 16.6, 8.4 Hz, 2H), 1.84 (m, 2H), 1.81 (d, J = 4.0 Hz, 1H), 1.72 (ddd, J = 16.0, 8.0, 4.0 Hz, 2H), 1.51 (m, 2H).

The compounds in Table 1 below were prepared using conditions similar to those in the above examples. The structural characterization data of these compounds are also listed in Table 1.

Table 1

Compound No.	^{1}HNMR data or structure and ^{1}HNMR
Cpd-03	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.78 (s, 1H), 10.79 (s, 1H), 9.95 (s, 1H), 7.66 (d, J = 12.8 Hz, 1H), 7.51 (s, 1H), 6.49 (d, J = 7.9 Hz, 1H), 1.26 (s, 9H).
Cpd-04A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.18 (s, 1H), 10.65 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 2.58 (dd, J = 14.1, 6.6Hz, 1H), 1.71 – 1.57 (m, 1H), 1.46 (dd, J = 14.1, 6.8 Hz, 1H), 1.12 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H).
Cpd-04B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.18 (s, 1H), 10.64 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 2.58 (dd, J = 14.0, 6.9Hz, 1H), 1.63 (dq, J = 15.0, 7.5 Hz, 1H), 1.50 – 1.40 (m, 1H), 1.11 (d, J = 6.8 Hz, 3H), 0.85 (t, J = 7.4 Hz, 3H).
Cpd-09	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.49 (s, 1H), 10.63 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.4 Hz, 1H), 7.50 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 1.99 - 1.91 (m, 1H), 0.95 - 0.85 (m, 4H).
Cpd-11	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 10.67 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 3.42 – 3.34 (m, 1H), 2.33 – 2.10 (m, 4H), 2.04 – 1.76 (m, 2H).
Cpd-13	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 10.62 (s, 1H), 9.95 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 1.92 (dt, J = 13.9, 6.9Hz, 1H), 1.20 (d, J = 6.9 Hz, 3H), 0.99 – 0.90 (m, 1H), 0.55 – 0.47 (m, 1H), 0.44 – 0.36 (m, 2H), 0.19 – 0.11 (m, 1H).
Cpd-16	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.76 (s, 1H), 10.90 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.6 Hz, 1H), 7.53 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 5.81 (s, 1H), 1.39 (s,6H).
Cpd-18	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 10.56 (s, 1H), 9.93 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.56 (s, 1H), 6.51 (d, J = 7.6 Hz, 1H), 4.77 – 4.66 (m, 4H), 4.09 (s, 1H).
Cpd-19A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.19 (s, 1H), 10.62 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.87 – 3.78 (m, 1H), 3.14 (s, 3H), 2.93 – 2.84 (m, 1H), 2.46 – 2.41 (m, 2H), 2.11 – 2.02 (m, 2H).
Cpd-19B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.19 (s, 1H), 10.65 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.06 - 3.98 (m, 1H), 3.30 – 3.21 (m, 1H), 3.15 (s, 3H), 2.48 - 2.38 (m, 2H), 2.21 - 2.11 (m, 2H).
Cpd-22	^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.60 (d, J = 12.8 Hz, 1H), 7.51 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.01 – 3.95 (m, 2H), 3.89 (t, J = 8.9 Hz, 2H), 3.79 (dd, J = 16.5, 8.0Hz, 1H).
Cpd-34	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.13 (s, 1H), 10.63 (s, 1H), 9.95 (s, 1H), 7.61 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.59 (s, 2H), 4.51 (s,2H), 3.25 - 3.10 (m, 1H), 2.48 - 2.40 (m, 4H).
Cpd-35	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.03 (s, 1H), 10.94 (s, 1H), 9.92 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.37 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.67 (s, 4H), 4.19 (s,4H).

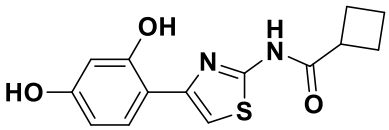
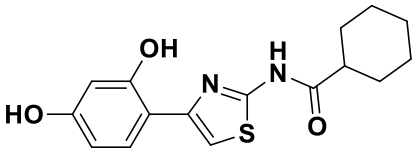
Cpd-36A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 10.61 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.54 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 3.93(t, J = 8.3 Hz, 1H), 3.83 – 3.68 (m, 3H), 3.32 – 3.26 (m, 1H), 2.19 – 2.05 (m, 2H).
Cpd-36B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.33 (s, 1H), 10.61 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.54 (s, 1H), 6.52 (d, J = 7.9 Hz, 1H), 3.94 (t,J = 8.3 Hz, 1H), 3.83 – 3.67 (m, 3H), 3.33 – 3.26 (m, 1H), 2.18 – 2.05 (m, 2H).
Cpd-40	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.17 (s, 1H), 11.64 (s, 1H), 11.06 (s, 1H), 8.14 (s, 1H), 7.59 (s, 1H), 6.58 (s, 1H), 2.79 – 2.71 (m, 1H), 1.13 (d, *J* = 6.9 Hz, 6H).
Cpd-41	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.17 (s, 1H), 9.42 (s, 1H), 7.56 (s, 1H), 7.38 (s, 1H), 6.38 (s, 1H), 2.79 – 2.71 (m, 1H), 2.05 (s, 3H), 1.13 (d, J = 6.9 Hz, 6H).
Cpd-42	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.14 (s, 1H), 10.79 (s, 1H), 10.29 (s, 1H), 8.03 (s, 1H), 7.53 (s, 1H), 6.58 (s, 1H), 2.79 – 2.70 (m, 1H), 1.13 (d, J = 6.9 Hz, 6H).
Cpd-44	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.99 (d, J = 27.4 Hz, 2H), 9.92 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.39 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.66 – 3.58 (m, 4H), 3.55 – 3.47 (m, 4H).
Cpd-45	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.22 (s, 1H), 10.67 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 3.95 –3.87 (m, 2H), 3.35 (td, J = 11.5, 2.1 Hz, 2H), 2.82 – 2.71 (m, 1H), 1.80 – 1.60 (m, 4H).
Cpd-46	^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.61 (d, J = 12.8 Hz, 1H), 7.51 (s, 1H), 6.52 (d, J = 8.0 Hz, 1H), 3.85 (s, 2H), 3.08 – 2.93 (m, 1H),1.88 (dd, J = 28.1, 16.4 Hz, 8H).
Cpd-47	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 10.66 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.55 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.28 –3.10 (m, 4H), 2.86 (ddd, J = 10.8, 7.6, 3.5 Hz, 1H), 2.25 (d, J = 11.2 Hz, 2H), 2.11 (dd, J = 19.2, 8.0 Hz, 2H).
Cpd-48A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.97 (s, 1H), 10.87 (s, 1H), 10.04 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.54 (s, 1H), 6.48 (d, J = 8.0 Hz, 1H), 4.12(d, J = 10.4 Hz, 1H), 4.01 (d, J = 10.8 Hz, 1H), 3.52 (dt, J = 13.2, 6.7 Hz, 1H), 1.96 – 1.78 (m, 2H), 1.53 (t, J = 9.6 Hz, 4H).
Cpd-49A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.09 (s, 1H), 10.75 (s, 1H), 9.96 (s, 1H), 7.64 (d, J = 12.8 Hz, 1H), 7.55 (s, 1H), 6.49 (d, J = 8.0 Hz, 1H), 4.56 (dd,J = 8.0, 5.5 Hz, 1H), 3.98 (dd, J = 14.4, 6.8 Hz, 1H), 3.84 (dd, J = 14.4, 6.7 Hz, 1H), 2.23 (ddd, J = 14.8, 12.3, 7.9 Hz, 1H), 2.00 (td, J = 12.4, 7.0 Hz,1H), 1.93 – 1.83 (m, 2H).
Cpd-49B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.08 (s, 1H), 10.74 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.55 (s, 1H), 6.49 (d, J = 8.0 Hz, 1H), 4.56 (dd,J = 8.0, 5.5 Hz, 1H), 3.98 (dd, J = 14.4, 7.0 Hz, 1H), 3.84 (dd, J = 14.4, 6.9 Hz, 1H), 2.23 (dt, J = 14.8, 7.8 Hz, 1H), 2.10 – 1.95 (m, 1H), 1.95 – 1.83(m, 2H).
Cpd-50A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 10.75 (s, 1H), 9.98 (s, 1H), 7.63 (d, J = 12.7 Hz, 1H), 7.57 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 4.41 (dd, J = 8.7, 3.1Hz, 1H), 4.00 – 3.85 (m, 2H), 3.75 – 3.67 (m, 2H), 3.66 – 3.54 (m, 2H).
Cpd-50B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 10.77 (s, 1H), 9.97 (s, 1H), 7.63 (d, J = 12.7 Hz, 1H), 7.56 (s, 1H), 6.49 (d, J =

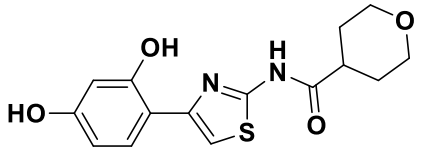
	8.0 Hz, 1H), 4.40 (dd, J = 8.7, 2.9Hz, 1H), 3.96 – 3.87 (m, 2H), 3.72 – 3.57 (m, 4H).
Cpd-51A	^{1}H NMR (400 MHz, DMSO-d6) δ 12.18 (s, 1H), 10.73(s,1H), 9.97 (s, 1H), 7.62 (d, J = 12.7 Hz, 1H), 7.51 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 3.25 (s, 3H), 3.16 –3.07 (m, 1H), 2.47 – 2.41 (m, 1H), 2.12 – 2.01 (m, 2H), 1.91 (d, J = 11.4 Hz, 2H), 1.54 – 1.40 (m, 2H), 1.19 – 1.06 (m, 2H).
Cpd-54	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.88 (s, 1H), 10.74 (s, 1H), 9.95 (s, 1H), 7.66 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.50 (d, J = 7.9 Hz, 1H), 3.74 –3.64 (m, 2H), 3.44 (t, J = 9.0 Hz, 2H), 2.12 (d, J = 14.1 Hz, 2H), 1.59 – 1.50 (m, 2H), 1.30 (s, 3H).
Cpd-55	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.31 (s, 1H), 10.62 (s, 1H), 9.95 (s, 1H), 7.63 (d, J = 12.7 Hz, 1H), 7.54 (s, 2H), 6.51 (d, J = 7.9 Hz, 1H), 3.16 (d, J =8.7 Hz, 2H), 3.03 (td, J = 9.7, 3.3 Hz, 1H), 2.39 – 2.32 (m, 2H), 2.07 – 1.97 (m, 1H), 1.85 – 1.72 (m, 1H).
Cpd-55A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.31 (s, 1H), 10.62 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.54 (s, 2H), 6.52 (d, J = 8.0 Hz, 1H), 3.17 (s,2H), 3.03 (d, J = 8.4 Hz, 1H), 2.34 (dd, J = 14.8, 11.3 Hz, 2H), 2.02 (d, J = 9.7 Hz, 1H), 1.86 – 1.70 (m, 1H).
Cpd-55B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.30 (s, 1H), 10.63 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.54 (s, 2H), 6.51 (d, J = 8.0 Hz, 1H), 3.17(s, 2H), 3.03 (d, J = 8.4 Hz, 1H), 2.40 – 2.33 (m, 2H), 2.02 (dd, J = 13.2, 3.6 Hz, 1H), 1.89 – 1.70 (m, 1H).
Cpd-56	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.31 (s, 1H), 10.62 (s, 1H), 9.94 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.54 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.35 –3.23 (m, 2H), 3.11 – 2.99 (m, 1H), 2.82 (s, 3H), 2.43 (t, J = 7.2 Hz, 2H), 2.15 – 2.04 (m, 1H), 1.89 (ddd, J = 19.2, 12.5, 7.8 Hz, 1H).
Cpd-57	1H NMR (400 MHz, DMSO-*d6*) δ 10.95 (s, 1H), 9.93 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.36 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.99 (s, 4H), 2.15 (t, J = 7.6 Hz, 4H), 1.81 – 1.76 (m, 2H).
Cpd-58A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 10.90 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.32 – 4.16 (m, 1H),3.94 – 3.75 (m, 1H), 3.66 (d, J = 11.5 Hz, 1H), 3.59 – 3.52 (m, 2H), 3.40 – 3.35 (m, 1H), 3.23 – 3.12 (m, 1H), 1.22 (d, J = 6.7 Hz, 3H).
Cpd-59A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 10.94 (s, 1H), 9.93 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.39 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.03 (dd, J = 27.2,13.0 Hz, 2H), 3.85 (dd, J = 11.6, 2.5 Hz, 1H), 3.52 – 3.43 (m, 2H), 3.06 – 2.84 (m, 1H), 2.72 – 2.53 (m, 1H), 1.12 (d, J = 6.2 Hz, 3H).
Cpd-60A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.25 (s, 1H), 10.63 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.97 (d, J = 10.4 Hz,1H), 3.80 (d, J = 11.2 Hz, 1H), 3.43 (t, J = 10.8 Hz, 1H), 3.34 (t, J = 11.2 Hz, 1H), 2.78 (t, J = 10.4 Hz, 1H), 1.97 (d, J = 12.0 Hz, 1H), 1.75 -1.63 (m, 2H), 1.58 – 1.49 (m, 1H).
Cpd-60B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.26 (s, 1H), 10.64 (s, 1H), 9.97 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 3.97(dd, J = 11.1, 2.7 Hz, 1H), 3.80 (d, J = 11.2 Hz, 1H), 3.48 – 3.39 (m, 2H), 2.84 – 2.72 (m, 1H), 1.98 (d, J = 11.2 Hz, 1H), 1.79 – 1.61 (m, 2H), 1.60 – 1.47 (m, 1H).

Cpd-61	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.12 (s, 1H), 10.67 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.35 (s, 2H), 3.09 –2.94 (m, 1H), 1.90 - 1.70 (m, 6H), 1.66 -1.58 (m, 2H).
Cpd-62	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.11 (s, 1H), 10.73 (s, 1H), 10.09 (s, 1H), 7.61 (d, J = 12.8 Hz, 1H), 7.51 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 3.56 – 3.49 (m, 2H),3.46 – 3.42 (m, 2H), 3.34 (s, 1H), 2.10 - 2.00 (dd, J = 14.7, 5.8 Hz, 4H), 1.62 – 1.57 (m, 2H), 1.53 – 1.48 (m, 2H).
Cpd-63	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.09 (s, 1H), 10.93 (s, 1H), 9.92 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.36 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 4.34 (s, 4H), 3.50 –3.40 (m, 4H), 1.84 – 1.75 (m, 4H).
Cpd-64A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.14 (s, 1H), 10.70 (s, 1H), 9.94 (s, 1H), 7.62 (d, J = 12.0 Hz, 1H), 7.50 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.59 (d, J = 4.0 Hz,1H), 3.37 (d, J = 4.0 Hz, 1H), 2.33 (d, J = 4.0 Hz, 1H), 1.87 (m, 5H), 1.45 (m, 3H).
Cpd-64B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.11 (s, 1H), 10.73 (s, 1H), 9.94 (s, 1H), 7.62 (d, J = 12.0 Hz, 1H), 7.50 (s, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.79 (s, 1H), 1.24 (s, 6H).
Cpd-66	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.19 (s, 1H), 10.69 (s, 1H), 8.16 (s, 1H), 7.62 (d, J = 12.78Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 4.52 (t, J = 6.8 Hz, 2H), 4.43 (t, J = 6.4 Hz, 2H), 3.41 – 3.37 (m, 1H), 2.84 - 2.71 (m, 2H), 2.48 - 2.45 (m, 1H), 1.88 - 1.75 (m, 4H), 1.70 - 1.62 (m, 2H).
Cpd-67	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.44 (s, 1H), 10.07 (s, 1H), 9.26 (s, 1H), 9.01 (d, J = 8.4 Hz, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.55 (s, 1H), 6.61 (d, J = 8.0 Hz,1H), 3.31 (d, J = 12.4 Hz, 2H), 3.01 – 2.80 (m, 3H), 2.03 (d, J = 12.0 Hz, 2H), 1.97 – 1.80 (m, 2H).
Cpd-68	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.25 (s, 1H), 10.66 (s, 1H), 9.96 (s, 1H), 7.63 (d, J = 12.8 Hz, 1H), 7.53 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.38 (d, J = 13.1 Hz,1H), 3.87 (d, J = 13.6 Hz, 1H), 3.35 (s, 3H), 3.08 (t, J = 11.6 Hz, 1H), 2.85 -2.70 (m, 1H), 2.61 (t, J = 11.5 Hz, 1H), 1.86 (t, J = 12.4 Hz, 2H), 1.60 (qd, J = 12.4, 4.1 Hz, 1H), 1.44 (qd, J = 12.4, 4.2 Hz, 1H).
Cpd-71	^{1}H NMR (400 MHz, MeOD-*d4*) δ 7.42 (d, J = 12.3 Hz, 1H), 7.25 (s, 1H), 6.39 (d, J = 8.0Hz, 1H), 3.78 (d, J = 11.9 Hz, 2H), 2.90 (s, 2H), 2.85 (s, 3H), 2.65 (s, 1H), 2.02 (d, J = 12.2 Hz, 2H), 1.91 – 1.81 (m, 2H).
Cpd-73A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.62 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.53 (d, J = 8.0 Hz, 1H), 3.31 (d, J = 12.0 Hz, 3H), 3.11 (s, 2H), 2.25 – 2.13 (m, 1H), 2.05 (dd, J = 13.2, 7.2 Hz, 1H).
Cpd-73B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.61 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.53 (d, J = 8.0 Hz, 1H), 3.25 (s, 2H), 3.10 (d, J = 42.8 Hz, 3H), 2.12 (s,1H), 2.00 (d, J = 5.8 Hz, 1H).
Cpd-77	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.04 (s, 1H), 10.86 (s, 1H), 9.93 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.37 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 4.36 (s, 2H), 3.78(d, J = 12.5 Hz, 2H), 3.07 (d, J = 11.5 Hz, 2H), 1.76 (ddd, J = 20.0, 11.6, 5.7 Hz, 4H).
Cpd-78	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.98 (s, 2H), 9.93 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.39 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.42 (s, 2H), 3.63 – 3.52 (m, 4H),1.88 (dt, J = 11.3, 8.1 Hz, 4H).

Cpd-79	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.06 (s, 1H), 10.77 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.23 (s, 1H), 4.00 (s, 2H), 3.90 (d, J = 8.6 Hz, 1H), 3.80 (s, 1H), 3.58 (s, 1H), 2.03 – 1.82 (m, 3H), 1.74 (d, J = 12.3 Hz, 1H).
Cpd-80A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.99 (s, 1H), 10.91 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.39 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.96 (td, J = 6.3, 3.4Hz, 2H), 3.60 (dd, J = 13.0, 3.1 Hz, 2H), 3.24 (dd, J = 13.1, 6.3 Hz, 2H), 1.12 (d, J = 6.4 Hz, 6H).
Cpd-80B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 10.92 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.08 (d, J= 12.4 Hz, 2H), 3.53 (ddd, J = 10.4, 6.4, 2.0 Hz, 2H), 2.54 (d, J = 14.0 Hz, 2H), 1.12 (s, 3H), 1.11 (s, 3H).
Cpd-81A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 10.78 (s, 1H), 9.91 (s, 1H), 7.60 (d, J = 12.6 Hz, 1H), 7.38 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 4.12 (s, 2H), 3.73 (d, J = 11.4 Hz, 2H), 3.54 (d, J = 10.6 Hz, 2H), 1.29 (d, J = 6.0 Hz, 6H).
Cpd-81B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.21 (s, 1H), 10.95 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.0 Hz, 1H), 7.42 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.79 (dd, J = 16, 8Hz, 2H), 3.44 (dd, J = 16, 5.38 Hz, 2H), 1.17 (s, 3H), 1.16 (s, 3H).
Cpd-84	1H NMR (400 MHz, DMSO-*d6*) δ 10.91 (s, 2H), 9.92 (s, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.39 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 3.68 – 3.63 (m, 2H),3.51 – 3.45 (m, 2H), 3.37 (s, 2H), 1.16 (s, 6H).
Cpd-86	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.19 (s, 1H), 10.80 (s, 1H), 9.92 (s, 1H), 7.61 (d, J = 12.7 Hz, 1H), 7.41 (s, 1H), 6.48 (d, J = 7.9 Hz, 1H), 4.39 (s, 2H), 4.10 (d, J = 10.6 Hz, 2H), 3.76 (d, J = 10.5 Hz, 2H), 2.62 (dd, J = 13.8, 6.8 Hz, 1H), 1.71 (d, J = 8.3 Hz, 1H).
Cpd-103	^{1}H NMR (400 MHz, MeOD-*d4*) δ 7.45 (d, J = 12.0 Hz, 1H), 7.30 (s, 1H), 6.42 (d, J = 7.8 Hz, 1H), 4.28 (t, J = 10.6 Hz, 2H), 4.16 (t, J = 8.7 Hz, 2H), 3.63 – 3.52(m, 2H), 3.38 (s, 3H), 3.37 – 3.33 (m, 2H), 3.24 (ddd, J = 14.7, 8.4, 6.3 Hz, 1H), 2.78 - 2.40 (m, 4H).
Cpd-107	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.01 (s, 1H), 10.93 (s, 1H), 9.91 (s, 1H), 7.59 (d, *J* = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, *J* = 8.0 Hz, 1H), 4.22 (s, 3H), 3.83 (d, *J* = 6.4 Hz, 2H), 3.22 (s, 3H).
Cpd-108	^{1}H NMR (400 MHz, DMSO-*d6*) δ 7.58 (d, J = 12.7 Hz, 1H), 7.35 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 4.10 (d, J = 8.3 Hz, 2H), 4.03 (s, 2H), 3.21 (d, J = 8.6 Hz, 1H).
Cpd-109	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 10.88 (s, 1H), 9.91 (s, 1H), 7.60 (d, J = 12.7 Hz, 1H), 7.39 (s, 1H), 6.47 (d, J = 8.0 Hz, 1H), 4.23 (t, J = 8.8 Hz, 2H), 4.15 – 4.03 (m, 2H), 3.68 (s, 3H), 3.54 (ddd, J = 14.7, 9.0, 5.8 Hz, 1H).
Cpd-110	^{1}H NMR (400 MHz, DMSO-*d6*) δ 10.97 (d, J = 26.0 Hz, 2H), 9.92 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.49 (s, 1H), 7.37 (s, 1H), 7.05 (s, 1H), 6.46 (d, J = 8.0 Hz,1H), 4.12 (t, J = 7.9 Hz, 2H), 4.07 – 3.97 (m, 2H), 3.30 – 3.27 (m, 1H).
Cpd-111	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.04 (s, 1H), 10.94 (s, 1H), 9.91 (s, 1H), 7.59 (d, J = 12.7 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 7.9 Hz, 1H), 4.19 (t, J = 8.3 Hz, 2H), 4.14 – 4.04 (m, 2H), 3.78 – 3.69 (m, 1H), 2.86 (d, J = 3.3 Hz, 6H).

Cpd-112	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.52 (s, 1H), 10.03 (s, 1H), 9.42 (s, 1H), 7.25 (d, J = 12..0 Hz, 1H), 7.18 (s, 1H), 6.22 (d, J = 7.6 Hz, 1H), 5.71 (tt, J = 52.0, 3.6 Hz,1H), 3.47 (s, 3H), 3.32 (s, 2H), 2.79 (td, J = 15.0, 3.8 Hz, 2H).
Cpd-116A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.15 (s, 2H), 10.64 (s, 1H), 9.96 (s, 1H), 7.62 (d, J = 12.78Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 3.26 (d, J = 8.8 Hz, 1H), 3.06 (p, J = 9.2 Hz, 1H), 2.36 (t, J = 8.8 Hz, 4H).
Cpd-116B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.14 (s, 1H), 10.68 (s, 1H), 7.61 (d, J = 12.8 Hz, 1H), 7.52 (s, 1H), 6.50 (d, J = 8.0 Hz, 1H), 3.40 (d, J = 7.2Hz, 1H), 3.08 – 3.00 (m, 1H), 2.45 - 2.28 (m, 4H).
Cpd-118A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.17 (s, 1H), 10.69 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.0 Hz, 1H), 7.51 (s, 1H), 6.50 (d, J = 4.0 Hz, 1H), 2.33 (s, 2H), 1.47 (m, 3H), 1.40 -1.30 (m, 3H), 1.24 (s, 2H).
Cpd-126	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.22 (s, 1H), 10.65 (s, 1H), 10.00 (s, 1H), 7.62 (d, J = 12.8 Hz, 1H), 7.51 (s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 3.82 (d, J = 7.6 Hz,2H), 3.27 (s, 2H), 2.40 (d, J = 7.1 Hz, 2H), 2.08 – 2.01 (m, 1H), 1.57 (d, J = 10.4 Hz, 2H), 1.29 – 1.21 (m, 2H).
Cpd-131	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.88 (s, 1H), 10.95 (s, 1H), 9.47 (s, 1H), 7.68(d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 6.31-6.28 (m, 2H), 3.70-3.66 (m, 2H), 3.46-3.41(m, 2H), 2.17-2.06 (m, 2H), 1.55-1.51 (m, 2H), 1.30 (s, 3H)
Cpd-132	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.39 (s, 1H), 10.87 (s, 1H), 9.49 (s, 1H), 7.66 (d, J = 8.2 Hz, 1H), 7.44 (s, 1H), 6.35 – 6.27 (m, 2H), 3.20 (d, J = 19.8 Hz, 4H),2.84 (d, J = 10.4 Hz, 1H), 2.25 (d, J = 11.3 Hz, 2H), 2.11 (dd, J = 20.7, 9.8 Hz, 2H).
Cpd-134A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.23 (s, 1H), 10.65 (s, 1H), 9.95 (s, 1H), 7.63 (d, J = 12.7 Hz, 1H), 7.55 (s, 1H), 6.51 (d, J = 7.9 Hz, 1H), 3.93 – 3.83 (m, 1H), 3.58 – 3.49 (m, 1H), 2.80 – 2.71 (m, 2H), 2.62 – 2.52 (m, 2H).
Cpd-134B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.23 (s, 1H), 10.61 (s, 1H), 9.95 (s, 1H), 7.62 (d, J = 12.4 Hz, 1H), 7.54 (s, 1H), 6.51 (d, J = 8.2 Hz, 1H), 3.89 – 3.80 (m, 1H),3.49 – 3.45 (m, 1H), 2.67 – 2.55 (m, 4H).
Cpd-135A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.44 (s, 1H), 6.32-6.29 (m, 2H), 3.91-3.85 (m, 1H), 3.58-3.50 (m, 1H), 2.80-2.73 (m, 2H), 2.58-2.50 (m, 2H).
Cpd-135B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.24 (s, 1H), 10.83 (s, 1H), 9.48 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.43 (s, 1H), 6.32-6.29 (m, 2H), 3.86-3.82 (m, 1H), 3.49-3.45 (m, 1H), 2.65-2.55 (m, 4H).
Cpd-137	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.35 (s, 1H), 10.81 (s, 1H), 9.49 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 6.34-6.30 (m, 2H), 2.57 (s, 6H).
Cpd-138	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.35 (s, 1H), 10.81 (s, 1H), 9.49 (s, 1H), 7.69 (d, J = 8.4 Hz, 1H), 7.46 (s, 1H), 6.34-6.30 (m, 2H), 2.57 (s, 6H).
Cpd-139A	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 10.84 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.37 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 3.90 (d, J = 28.4 Hz, 2H), 3.68 – 3.55 (m, 3H), 2.18 (s, 2H).

Cpd-139B	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.08 (s, 1H), 10.84 (s, 1H), 9.91 (s, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.37 (s, 1H), 6.45 (d, J = 8.0 Hz, 1H), 3.94 (d, J = 8.4 Hz,2H), 3.69 (s, 3H), 2.18 (s, 2H).
Cpd-140	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.07 (s, 1H), 11.00 (s, 1H), 9.92 (s, 1H), 7.60 (d, J = 12.8 Hz, 1H), 7.38 (s, 1H), 6.46 (d, J = 8.0 Hz, 1H), 4.21 (d, J= 13.6 Hz, 2H), 3.33 (t, J = 11.2 Hz, 1H), 3.12 (t, J = 11.6 Hz, 2H), 2.11 – 1.99 (m, 2H), 1.78 – 1.62 (m, 2H).
Cpd-144A	^{1}H NMR (400 MHz, DMSO-*d6*) δ12.15 (s, 1H), 10.85 (s, 1H), 9.48 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 6.30 (dt, J = 8.3, 2.3 Hz, 2H), 5.21 (d, J = 7.0Hz, 1H), 4.02 (dd, J = 15.1, 8.1 Hz, 1H), 2.75 (td, J = 9.7, 4.9 Hz, 1H), 2.40 (ddd, J = 15.2, 7.4, 2.8 Hz, 2H), 2.11 – 2.00 (m, 2H).
Cpd-144B	^{1}H NMR (400 MHz, DMSO-*d6*) δ12.15 (s, 1H), 10.88 (s, 1H), 9.48 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.41 (s, 1H), 6.34 – 6.25 (m, 2H), 5.17 (d, J = 6.3 Hz, 1H), 4.30 (dd, J = 13.5, 6.8 Hz, 1H), 3.24 – 3.15 (m, 1H), 2.43 (ddd, J = 12.8, 7.0, 3.5 Hz, 2H), 2.15 – 2.08 (m, 2H).
Cpd-151	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.27 (s, 1H), 9.42 (s, 1H), 7.50 (d, *J* = 8.5 Hz, 1H), 7.06 (s, 1H), 6.36 – 6.02 (m, 2H), 5.32 (s, 1H), 3.46 (d, *J* = 41.6 Hz, 2H), 2.00 (d, *J* = 7.2 Hz, 2H), 1.46 (s, 1H), 0.85 (d, *J* = 6.6 Hz, 1H).
Cpd-152	^{1}H NMR (400 MHz, DMSO-*d6*) δ 11.74 (s, 1H), 11.17 (s, 1H), 9.48 (s, 1H), 7.62 (d, *J* = 8.4 Hz, 1H), 7.41 (s, 1H), 6.35 (d, *J* = 30.0 Hz, 1H), 6.28 (s, 2H), 2.55 –2.52 (m, 2H), 2.20– 2.12 (m, 2H), 1.87 – 1.75 (m, 2H).
Cpd-154	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.16 (s, 1H), 10.95 (s, 1H), 9.51 (s, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.39 (s, 1H), 6.42 – 6.21 (m, 2H), 4.59 (s, 1H),4.37 (s, 1H), 3.79 (s, 1H), 1.87 (t, *J* = 12.4 Hz, 4H), 1.61 – 1.39 (m, 4H).
Cpd-155	^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.22 (s, 1H), 7.75 (d, *J* = 9.2 Hz, 1H), 7.48 (s, 1H), 7.08 (s, 1H), 6.57 (d, *J* = 5.2 Hz, 1H), 3.80 (d, *J* = 11.8 Hz,2H), 3.42 (dd, *J* = 21.6, 10.8 Hz, 2H), 2.12 – 2.01 (m, 2H), 1.70 (dd, *J* = 14.8, 7.3 Hz, 2H), 1.61 – 1.44 (m, 2H), 0.89 (dd, *J* = 16.0, 8.5 Hz, 3H).
Cpd-d1	 **Cpd-d1** ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.07 (s, 1H), 9.45 (s, 1H), 7.62 (d, J = 8.6 Hz, 1H), 7.25 (m, 1H), 6.28 (m, 2H), 2.27-2.19 (m, 2H), 2.15-2.13 (m, 2H), 2.03-1.92 (m, 2H), 1.83-1.81 (m, 1H).
Cpd-d2	 **Cpd-d2** ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.14 (s, 1H), 10.94 (s, 1H), 9.48 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.39 (s, 1H), 6.31-6.29 (m,

	2H), 1.84 (d, J = 12.0 Hz, 2H),1.76 (dd, J = 8.0, 4.0 Hz, 2H), 1.67 (s, 1H), 1.41 (d, J = 12.0 Hz, 2H), 1.29 (s, 1H), 1.23 (m, 3H).
Cpd-d3	 **Cpd-d3** ^{1}H NMR (400 MHz, DMSO-*d6*) δ 12.23 (s, 1H), 10.88 (s, 1H), 9.48 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.42 (s, 1H), 6.39 – 6.20 (m, 2H), 3.91 (d, J =11.2 Hz, 2H), 3.41 – 3.30 (m, 2H), 2.83 – 2.70 (m, 1H), 1.80 – 1.58 (m, 4H).

Biological Evaluation

Test Example 1 Inhibitory activity of the compounds of the present invention against human tyrosinase

1.1 Experimental materials

Experimental materials	Supplier
Human tyrosine protein (hTyr)	OriGene Technologies
L-DOPA	MCE
Thiamidol	MACKLIN

1.2 Experimental devices and instruments

Devices and instruments	Supplier
384-well plate	Corning
96-well polypropylene plate	Nunc
Plate shaker	Thermo
Centrifuge	Eppendorf
PHERAstar FSX	BMG LABTECH

1.3 Experimental steps

Step 1 Preparation of stock solutions of test compounds in DMSO: All compounds were reconstituted with DMSO to prepare 60 mM stock solutions. The solutions were stored in a desiccator for later use and kept at room temperature for short-term storage (maximum 3 months).

Step 2 Compound screening protocol

1) Thiamidol was serially diluted 3-fold starting from 20 mM to prepare DMSO solutions of Thiamidol of 10 concentrations (6.667 mM, 2.222 mM, 0.741 mM, 0.247 mM, 0.082 mM, 0.027 mM, 0.009 mM, 0.003 mM, 0.001 mM, 0.3 μM) and blank DMSO solution.

2) A volume of 100 nL diluted compound solution was transferred to each well of the assay plate using Echo 665.3, and the compound plate was centrifuged at 1000 rpm for 1 min.

3) 10 μL of 2× tyrosinase (TYR) working solution was added to the assay plate and the system was incubated at room temperature for 30 min. Then 10 μL of 2× L-DOPA working solution was added and the system was incubated at 37°C for 2 h.

4) The absorbance signal at 475 nm was read using a BMG plate reader.

Step 3 Data processing

The percentage inhibition is calculated as follows:

$\%inhibition=100-(Signal_{cmpd}-Signal_{Ave_PC})/(Signal_{Ave\text{-}VC}-Signal_{Ave_PC}) \times 100$

$Signal_{cmpd}$: Mean absorbance value of test compounds on the assay plate.

$Signal_{ave_pc}$: Mean absorbance value of positive control on the assay plate.

$Signal_{ave_vc}$: Mean absorbance value of negative control on the assay plate.

IC50 fitting calculation:

IC_{50} values were determined by non-linear regression fitting of percentage inhibition against the logarithm of compound concentrations using GraphPad Prism 8.0.

1.4. Experimental results

The specific experimental results are shown in Table 2.

Table 2 Inhibitory activity of the compounds of the present invention against human tyrosinase

Compound	IC_{50} (μM)
Hydroquinone	>100
Thiamidol	0.96
Cpd-01	0.34
Cpd-02	5.65
Cpd-03	0.408
Cpd-04A	0.493
Cpd-04B	0.589
Cpd-09	0.453
Cpd-11	0.397
Cpd-13	0.668
Cpd-16	0.358
Cpd-17A	0.19
Cpd-17B	0.18
Cpd-18	0.263
Cpd-19A	0.234
Cpd-19B	0.319
Cpd-22	0.263
Cpd-34	0.249
Cpd-35	0.146
Cpd-36A	0.208
Cpd-36B	0.202
Cpd-40	>100
Cpd-41	>100
Cpd-42	>100
Cpd-44	0.244
Cpd-45	0.191

Cpd-46	0.188
Cpd-47	0.262
Cpd-48A	0.613
Cpd-49A	0.567
Cpd-49B	0.236
Cpd-50A	0.709
Cpd-50B	0.45
Cpd-51A	0.694
Cpd-54	0.212
Cpd-55	0.154
Cpd-56	0.214
Cpd-57	0.75
Cpd-58A	0.437
Cpd-59A	0.291
Cpd-60A	0.282
Cpd-60B	0.359
Cpd-61	0.372
Cpd-62	0.463
Cpd-63	0.215
Cpd-64A	0.236
Cpd-64B	0.169
Cpd-66	0.101
Cpd-67	0.173
Cpd-68	0.193
Cpd-71	0.880
Cpd-73A	0.253
Cpd-73B	0.255
Cpd-77	0.469
Cpd-78	0.418
Cpd-79	0.234
Cpd-80A	0.448
Cpd-80B	0.752
Cpd-81A	0.955
Cpd-84	0.349
Cpd-86	0.139
Cpd-103	0.113
Cpd-107	0.150
Cpd-108	0.055
Cpd-109	0.162
Cpd-110	0.091

Cpd-111	0.137
Cpd-112	0.340
Cpd-114	0.068
Cpd-117A	0.051
Cpd-117B	0.068
Cpd-117C	0.066
Cpd-117D	0.050
Cpd-118A	0.109
Cpd-126	0.207
Cpd-131	0.30
Cpd-132	0.450
Cpd-134A	0.072
Cpd-134B	0.114
Cpd-135A	0.146
Cpd-135B	0.334
Cpd-137	0.086
Cpd-138	0.095
Cpd-139A	0.070
Cpd-140	0.096
Cpd-144A	0.348
Cpd-144B	0.463
Cpd-151	5.019
Cpd-152	4.571
Cpd-153A	0.967
Cpd-154	0.593
Cpd-155	89.130
Cpd-d1	1.429
Cpd-d2	1.742
Cpd-d3	0.610

The results indicate that the compounds disclosed in the present invention exert potent inhibitory activity against human tyrosinase.

Test Example 2 Evaluation of compounds on spontaneous and α-MSH-stimulated melanogenesis in B16F10A

2.1 Cell line

B16F10A (mouse melanoma cell line), culture medium: RPMI 1640 + 10% fetal bovine serum + 1% penicillin-streptomycin

2.2 Main reagents and consumables

Name	**Brand**	**Cat#**	**Storage conditions**
RPMI1640	Gibco	22400-089	4°C

Fetal bovine serum	Gibco	10091-148	-80°C
DPBS (phosphate buffered saline)	BBI	E607009-0500	4°C
DMSO (dimethyl sulfoxide)	BBI	A600163-0250	Room temperature
α-MSH	MCE	HY-P0252	-80°C
0.25% trypsin	Gibco	25200-072	-20°C
Penicillin-streptomycin (100×)	Cellmax	CPS101.02	-20°C
96-well flat bottom plate	Corning	3599	Room temperature
Phenol red-free DMEM	Gibco	21063-029	4°C

2.3 Main instruments:

Name	**Brand**	**Model**
Carbon dioxide incubator	ThermoFisher	371
Microplate reader	PerkinElmer	Envision
Cell counter	Countstar	IC1000

2.4 Experimental method:

1) The cells were rinsed once with DPBS, then dissociated using 0.25% trypsin solution, and centrifuged at 300 g for 4 min;

2) The cells were washed once with phenol red-free culture medium (phenol red-free DMEM + 10% fetal bovine serum + 1% penicillin-streptomycin);

3) The cells were resuspended in phenol red-free culture medium, seeded into 96-well flat bottom plates at 10,000 cells/200 Ml/well, and incubated at 37°C with 5% CO_2 for 24 h;

4) 2 Ml test compounds at various concentrations were added to the cells, and the cells were incubated at 37°C with 5% CO_2 for 30 min;

5) The cells were stimulated with 1 Ml α-MSH (final concentration 200 μM) for 96 h;

6) The color change of the culture medium was observed and photographed;

7) The cell supernatant was transferred to a new 96-well plate and the absorbance at 470 nm was read using a microplate reader.

2.5 Data processing

1) The positive control group was DMSO, and the negative control group was cell-free (pure culture medium);

2) The %inhibition was calculated according to the formula below:

%inhibition = 100 − (absorbance of compound − mean absorbance of negative control) / (mean absorbance of positive control − mean absorbance of negative control) × 100;

3) Dose-response curves of compounds: IC50 was calculated by non-linear regression (dose-response - variable slope) fitting the percentage inhibition against the logarithm of compound concentrations using GraphPad Prism 10.0.

2.6 Experimental results

The results of inhibitory effects of the compounds disclosed herein on melanogenesis in B16F10 cells are summarized in Table 3.

Table 3 The inhibitory activity of the compounds of the present invention on melanogenesis in B16F10 cells

Compound	IC_{50} (nM)
Thiamidol	86.7
Cpd-01	28.8
Cpd-17A	37.9
Cpd-17B	25.0
Cpd-36A	29.0
Cpd-45	32.6
Cpd-47	23.0
Cpd-54	31.1
Cpd-55A	34.6
Cpd-55B	27.8
Cpd-60A	32.5
Cpd-107	28.3
Cpd-109	30.1
Cpd-108	27.6
Cpd-116B	43.1
Cpd-117A	6.0
Cpd-117B	14.0
Cpd-117C	6.0
Cpd-117D	10.0
Cpd-118A	13.4
Cpd-131	29.3
Cpd-144A	44.5
Cpd-144B	46.5
Cpd-152	209.0
Cpd-d3	44.4

The results demonstrate that the compounds disclosed in the present invention exhibit potent inhibitory activity against melanogenesis in B16F10 cells.

Test Example 3 In vitro skin permeation study

3.1 Formulation composition

Table 4 Formulation

Name	Weight percentage (%)
Cpd-d3 or Cpd-131	0.2
Glycerol	7.0
Isopropyl palmitate	5.5
Ethylene glycol	4.5
Isononyl isononanoate	4.0
PEG100 glyceryl stearate	3.5
Ethanol	3.0
1,2-Hexanediol	2.5
Polydimethylsiloxane	2.0

Stearyl alcohol	1.8
Cetyl alcohol	1.2
Tapioca starch	4.5
LMW sodium hyaluronate	0.5
Sodium stearoyl glutamate	0.3
EDTA-2Na	0.2
Tocopheryl acetate	0.5
Phenoxyethanol	0.8
Sodium VC phosphate	1.0
Sodium hydroxide	Q.S.
Water	To 100

3.2 Transdermal test conditions

Skin: Dorsal skin of miniature pig

Temperature: 32±0.5°C

Receptor fluid: 20% ethanol in normal saline

Volume of receptor fluid: 12 ml

Sampling volume: 1 ml

Effective area: 1.76 cm^2

Dosing amount: Infinite dosing via sample loop, approximately 400 mg

Speed: 600 rpm

Sampling time points: 0.5, 4, 8, 12, 16, 20, 24 h

3.3 Experimental procedures

The miniature pig skin was thawed, rinsed with normal saline and blotted dry with filter paper before the test for subsequent use. The skin was clamped between the upper and lower chambers of a Franz diffusion cell with the stratum corneum facing upward. The sample was loaded into the sample loop, and the device was secured. The receptor fluid pre-equilibrated to 32±1°C was added into the receptor chamber. The diffusion cell was placed in a thermostatted water bath, and magnetic stirring was initiated. Samples were collected and analyzed at preset time points, and an equal volume of receptor fluid at the same temperature was replenished immediately afterwards.

3.4 Experimental results

Table 5 Permeation results at different time points

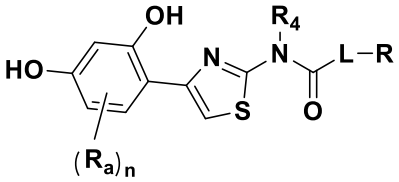
	Cumulative permeation per unit area μg/cm^2					
Compound	Cpd-d3			Cpd-131		
Cell	1	2	3	4	5	6
Skin thickness/mm	1.16	1.23	1.26	1.16	1.22	1.26
TEWL/μg/m^2/h	3.0	2.1	5.8	2.9	2.2	7.4
0.5h	0.000	0.000	0.000	0.000	0.000	0.000
4h	0.151	0.057	0.108	0.187	0.229	0.073
8h	0.932	0.444	0.681	1.151	1.316	0.576
12h	2.278	1.191	1.682	2.645	2.880	1.486
16h	3.899	2.254	2.952	4.336	4.635	2.612

20h	5.668	3.480	4.379	6.082	6.418	3.880
24h	7.522	4.838	6.010	7.824	8.213	5.185
Mean	6.12			7.07		

The results show that the compounds disclosed in the present invention possess favorable transdermal properties. Specifically, the compound Cpd-131 of the present invention exhibits better transdermal performance than the compound Cpd-d3.

CLAIMS

1. A compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof:



(I)

wherein the R_a groups are the same or different, and are each independently selected from H, OH, CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy or halo-C_{1-6} alkoxy;

L is absent, or is selected from C_{1-3} alkylene which is unsubstituted or optionally substituted with one, two or more L_a groups; the L_a groups are the same or different and are each independently selected from H or C_{1-6} alkyl;

R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: C_{1-12} alkyl, C_{3-12} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-14} aryl, 5- to 14-membered heteroaryl, $-NR_1R_2$ or $-OR_3$; wherein R_1, R_2 and R_3 are the same or different, and are each independently selected from H, C_{1-12} alkyl, C_{3-12} cycloalkyl, 3- to 14-membered heterocyclyl, C_{6-14} aryl or 5- to 14-membered heteroaryl;

the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-6} alkyl, C_{1-6} alkoxy, NH_2, $-S(=O)_2C_{1-6}$ alkyl, 3- to 8-membered heterocyclyl, $-C_{1-6}$ alkylene-O-C_{1-6} alkyl, $-C(=O)-R_5$, $-C(=O)OR_6$, $-C(=O)NR_7R_8$ or 5- to 14-membered heteroaryl; wherein R_5, R_6, R_7 and R_8 are the same or different, and are each independently selected from H or C_{1-6} alkyl;

alternatively, two R_b groups linked to different carbon atoms, together with the carbon atoms to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b1} groups: C_{3-8} carbocyclic rings or 3- to 8-membered heterocyclic rings;

alternatively, two R_b groups linked to the same carbon atom, together with the carbon atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: C_{3-8} carbocyclic rings or 3- to 8-membered heterocyclic rings;

the R_{b1} groups and R_{b2} groups are the same or different, and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-6} alkyl, C_{1-6} alkoxy, $-C_{1-6}$ alkylene-O-C_{1-6} alkyl or NH_2;

the R_{bb} groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), C_{1-6} alkyl, C_{1-6} alkoxy or NH_2;

R_4 is selected from H; alternatively, R_4 is linked to an atom on the R group to jointly form a heterocycle containing a lactam structure, the heterocycle is a 5- to 8-membered heterocycle which is unsubstituted or optionally substituted with one, two or more R_{4a} groups; the R_{4a} groups are the same or different and are each independently selected from OH, CN, halogen, oxo (=O), C_{1-6} alkyl, halo-C_{1-6} alkyl or C_{1-6} alkoxy;

n is selected from 0, 1, 2 or 3.

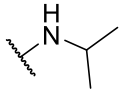
2. The compound according to claim 1, wherein the R_a groups are the same or different and are each independently selected from OH, CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy or halo-C_{1-6} alkoxy, and n is selected from 1, 2 or 3;

alternatively, the R_a groups are the same or different and are each independently selected from OH, CN, F, Cl, Br, methyl, trifluoromethyl or methoxy;

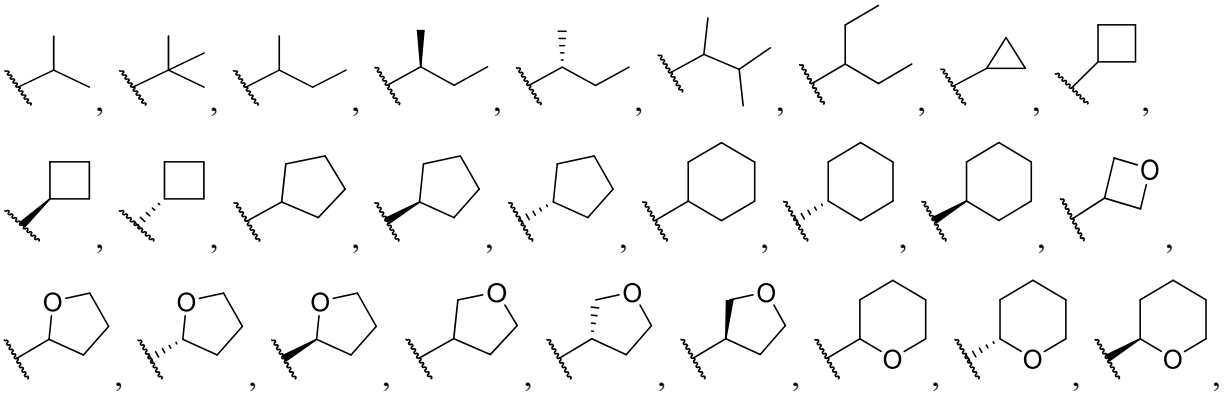
preferably, n is selected from 1;

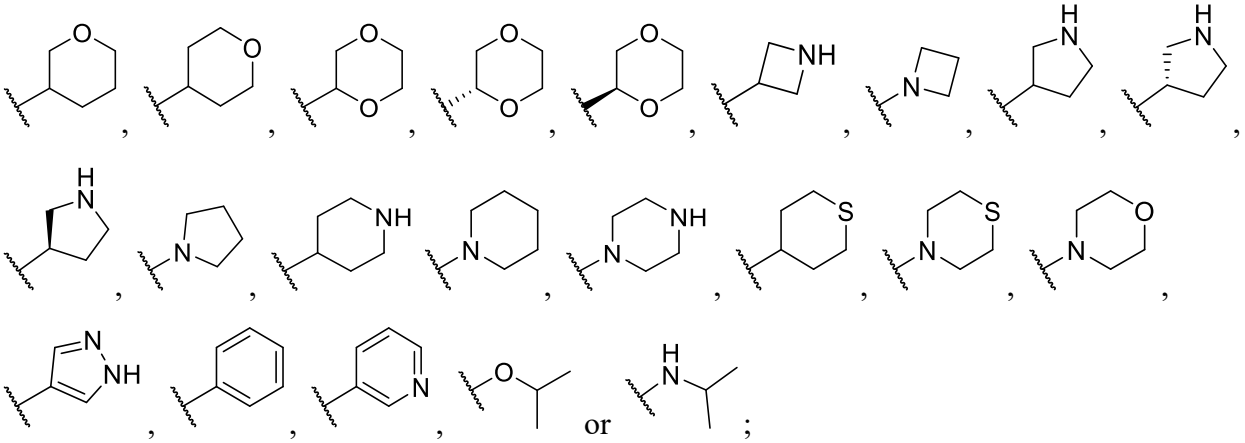
preferably, L is absent, or is selected from $-CH_2-$, $-CH_2CH_2-$ or $-CH(CH_3)-$.

3. The compound according to claim 1 or 2, wherein R_4 is selected from H, and R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: C_{1-6} alkyl, C_{1-6} alkoxy, C_{3-8} cycloalkyl, 3- to 8-membered heterocyclyl, C_{6-10} aryl, 5- to 10-membered heteroaryl, $-NR_1R_2$ or $-OR_3$;

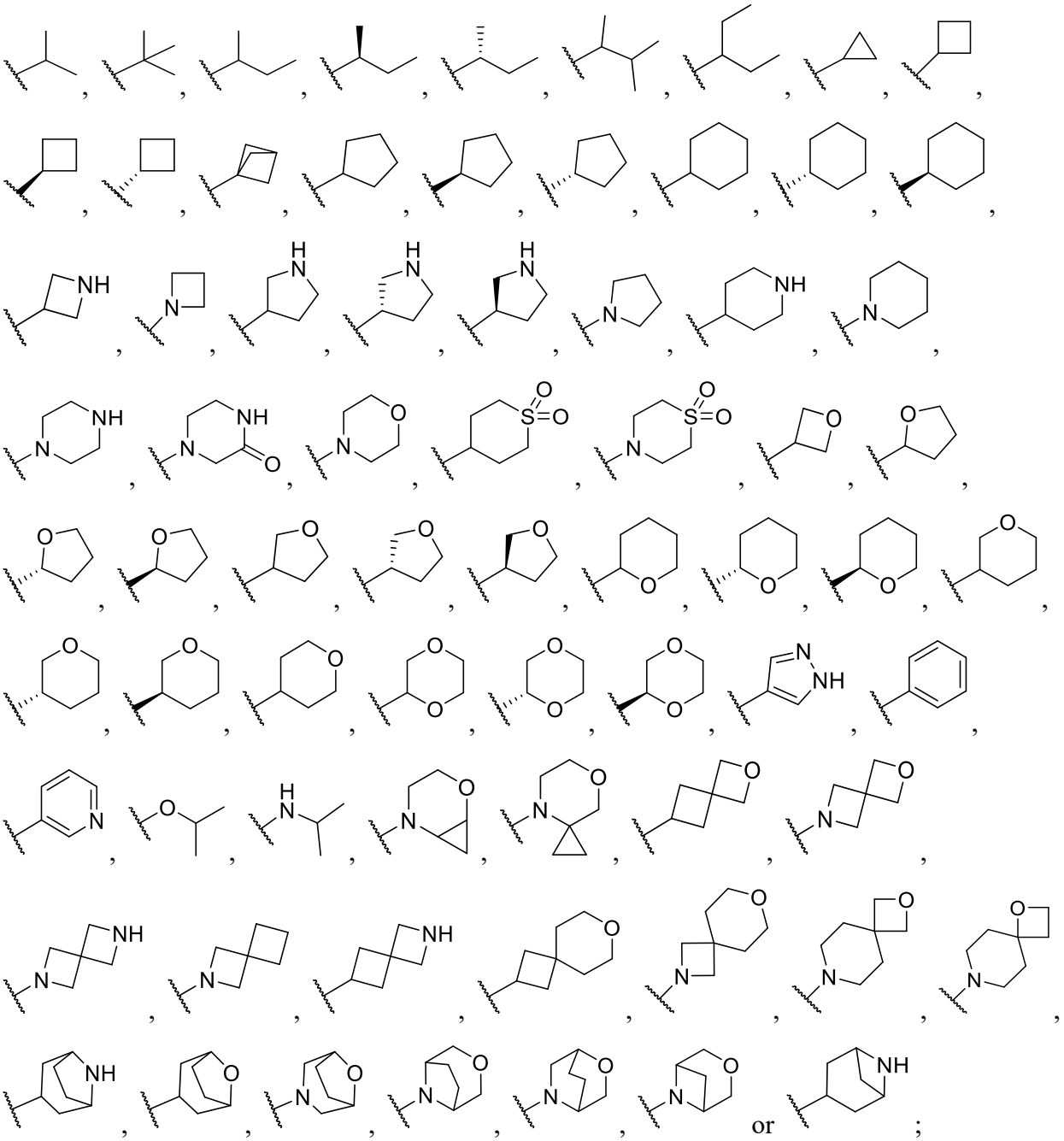
preferably, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups: methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, 3-methylbutan-2-yl, pentan-3-yl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, oxetanyl, tetrahydrofuryl, tetrahydro-2*H*-pyranyl, 1,4-dioxanyl, azetidinyl, pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, tetrahydro-2*H*-thiopyranyl, thiomorpholinyl, phenyl, pyridyl, pyrazolyl, isopropoxy or ;

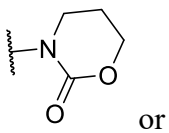
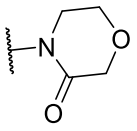
preferably, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups:





preferably, R is selected from the following groups which are unsubstituted or optionally substituted with one, two or more R_b groups:

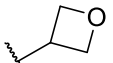
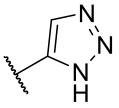
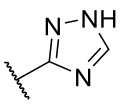


alternatively, R_4 is linked to an atom on the R group to jointly form  or .

4. The compound according to any one of claims 1 to 3, wherein the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-3} alkyl, C_{1-3} alkoxy, NH_2, $-S(=O)_2C_{1-3}$ alkyl, 3- to 8-membered heterocyclyl, $-C_{1-3}$ alkylene-O-C_{1-3} alkyl, $-C(=O)-R_5$, $-C(=O)OR_6$, $-C(=O)NR_7R_8$ or 5- to 6-membered heteroaryl;

preferably, R_5, R_6, R_7 and R_8 are the same or different, and are each independently selected from H or methyl;

preferably, the R_b groups are the same or different and are each independently selected from H, OH, CN, halogen, C_{1-6} alkyl, halo-C_{1-6} alkyl, C_{1-6} alkoxy or hydroxy-C_{1-6} alkyl (HO-C_{1-6} alkyl), $-C(=O)-C_{1-6}$ alkyl, $-S(=O)_2C_{1-6}$ alkyl, 3- to 6-membered heterocyclyl, $-C_{1-6}$ alkyl-O-C_{1-6} alkyl, $-C(=O)OH$, $-C(=O)OC_{1-6}$ alkyl, $-C(=O)NH_2$, $-C(=O)N(C_{1-6}$ alkyl$)_2$, $-C_{1-6}$ alkylene-O-halo-C_{1-6} alkyl, 5- to 6-membered heteroaryl;

preferably, the R_b groups are the same or different and are each independently selected from H, OH, CN, F, Cl, Br, methyl, ethyl, methoxy, hydroxymethyl, hydroxyethyl (e.g., 1-hydroxyethyl, 2-hydroxyethyl), oxo (=O), difluoromethyl, acetyl, methanesulfonyl, oxetanyl (e.g., ), methoxyethyl, 2,2-difluoroethyl, 2,2,2-trifluoroethyl, $-C(=O)OH$, $-C(=O)OCH_3$, $-C(=O)NH_2$, $-C(=O)N(CH_3)_2$, $-CH_2CH_2OCH_2CF_3$ or $-CH_2CH_2OCH_2CHF_2$, triazolyl (e.g., , ), tetrazolyl or isoxazol-3(2*H*)-keto;

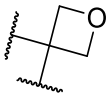
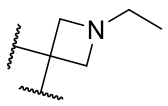
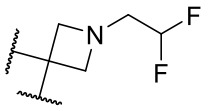
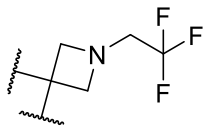
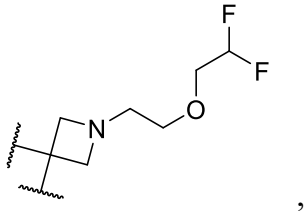
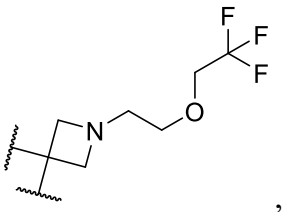
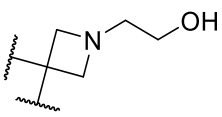
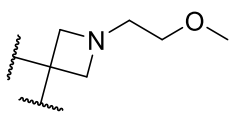
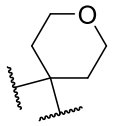
alternatively, the R_b groups linked to two adjacent carbon atoms, together with the atoms to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b1} groups: C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl or a 3- to 8-membered heterocycle;

alternatively, the R_b groups linked to two non-adjacent carbon atoms are linked via their terminal groups to jointly form C_{1-3} alkylene (e.g., $-CH_2-$, $-CH_2CH_2-$);

alternatively, the two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: C_{3-8} cycloalkyl, C_{3-8} cycloalkenyl or a 3- to 8-membered heterocycle;

preferably, the R_b groups linked to two adjacent carbon atoms, together with the atoms to which they are linked, jointly form a cyclopropane ring;

preferably, two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form the following groups which are unsubstituted or optionally substituted with one, two or more R_{b2} groups: a cyclopropane ring, a cyclobutane ring, an oxetane ring, an azetidine ring or a tetrahydro-2*H*-pyran ring;

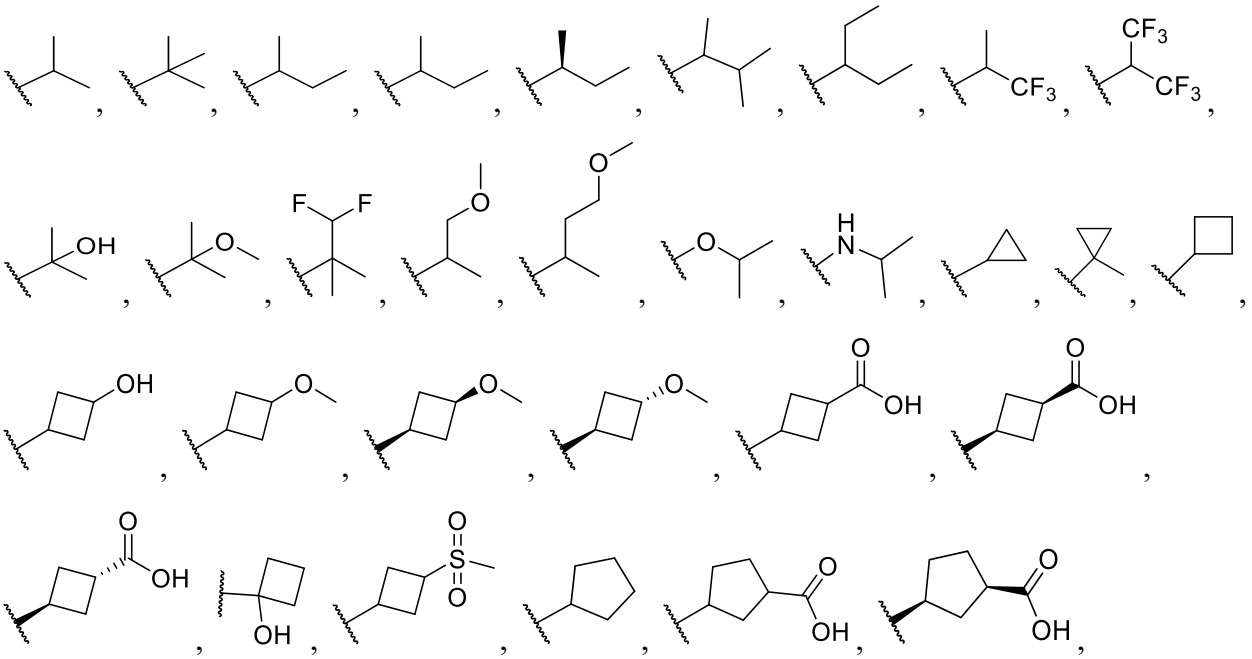
preferably, two R_b groups linked to the same carbon atom, together with the atom to which they are linked, jointly form a cyclopropane ring, a cyclobutane ring, an oxetane ring (e.g., ), , , , , , ,  or ;

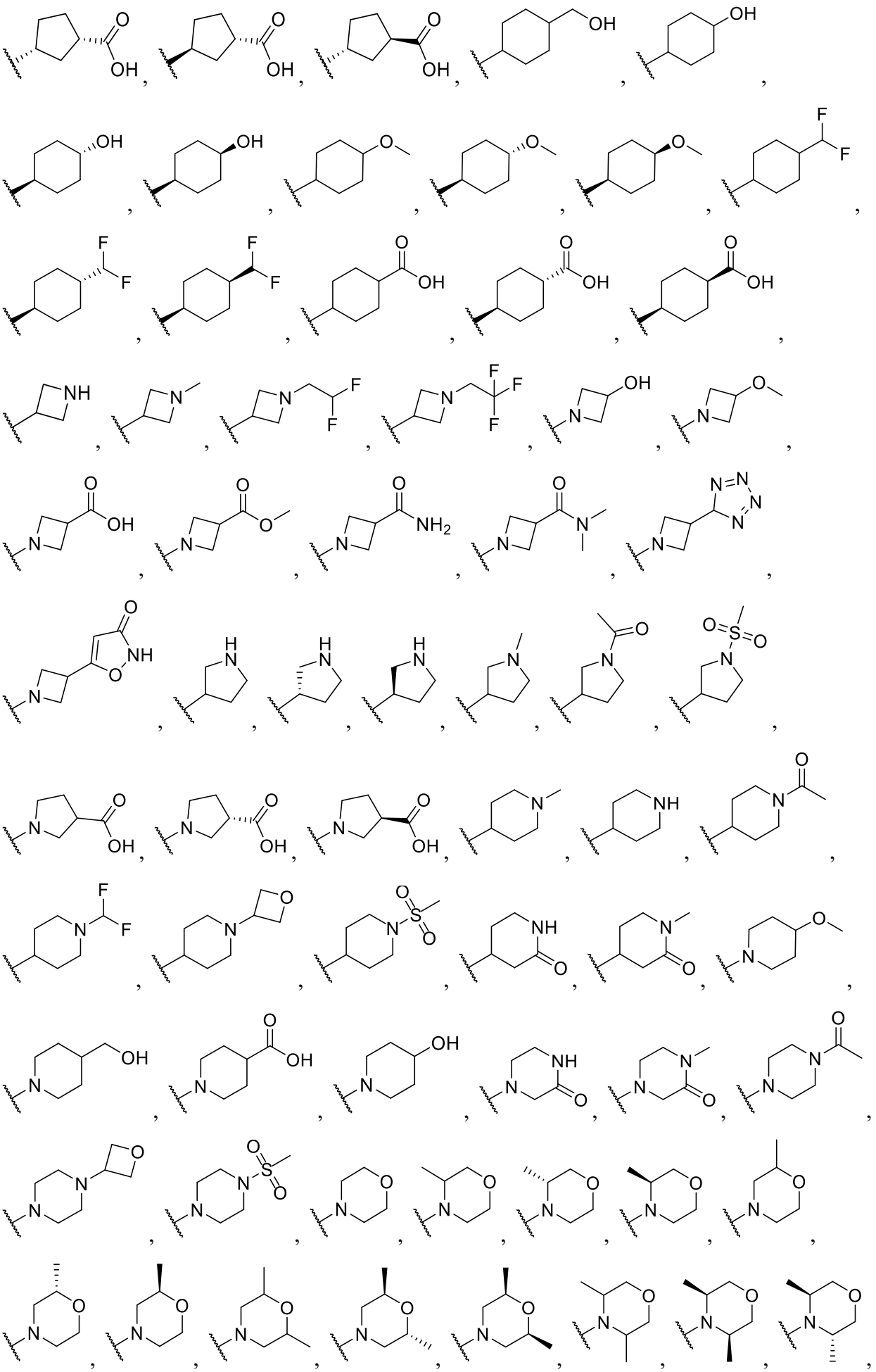
preferably, the R_{b1} groups and R_{b2} groups are the same or different, and are each independently selected from OH, CN, halogen, oxo (=O), and the following groups which are unsubstituted or optionally substituted with one, two or more R_{bb} groups: C_{1-3} alkyl, C_{1-3} alkoxy or NH_2;

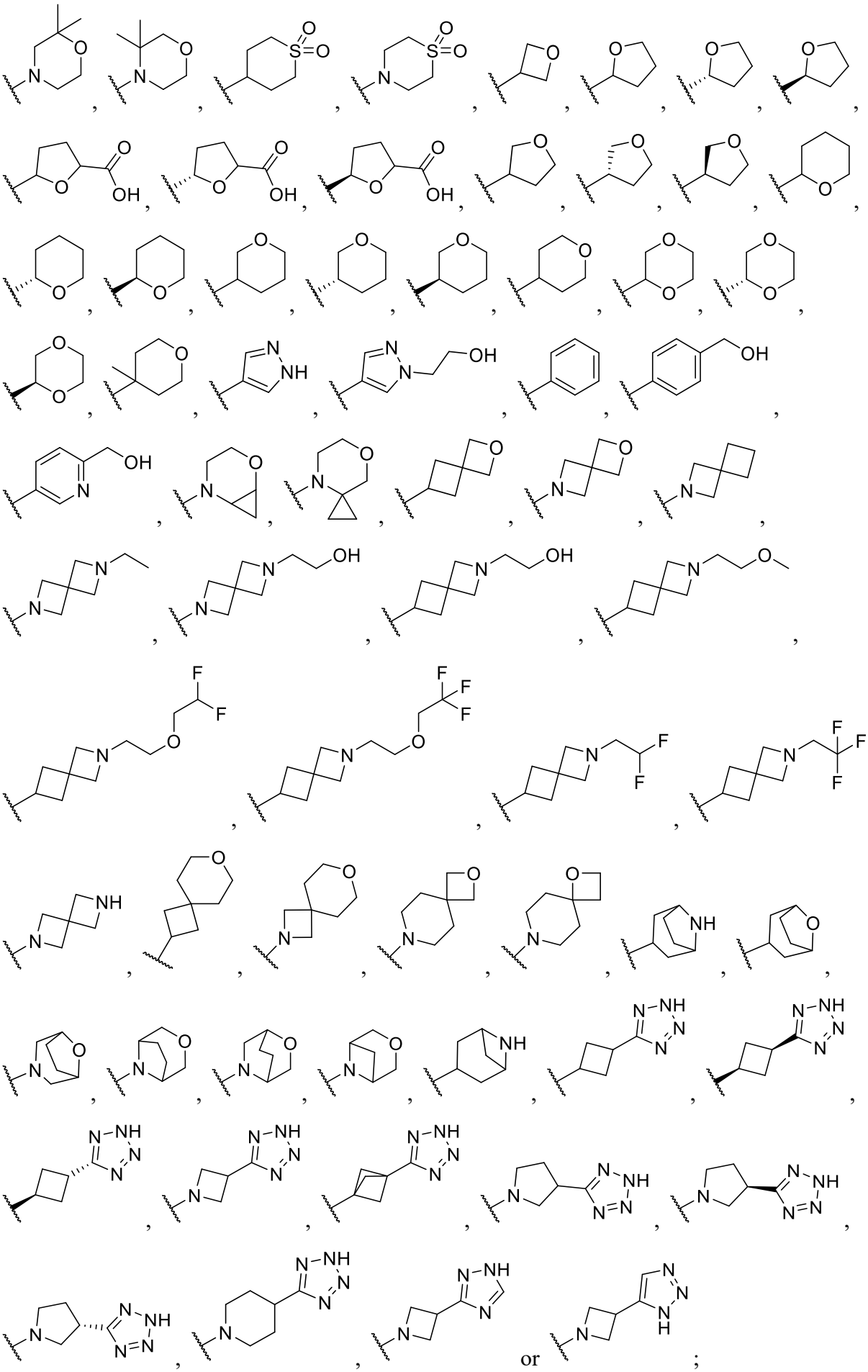
preferably, the R_{bb} groups are the same or different and are each independently selected from H, OH, CN, C_{1-6} alkoxy (e.g., methoxy) or halogen (e.g., F, Cl, Br);

more preferably, the R_{b2} groups are the same or different and are each independently selected from methyl, ethyl, hydroxyethyl (e.g., 1-hydroxyethyl, 2-hydroxyethyl) or methoxyethyl;

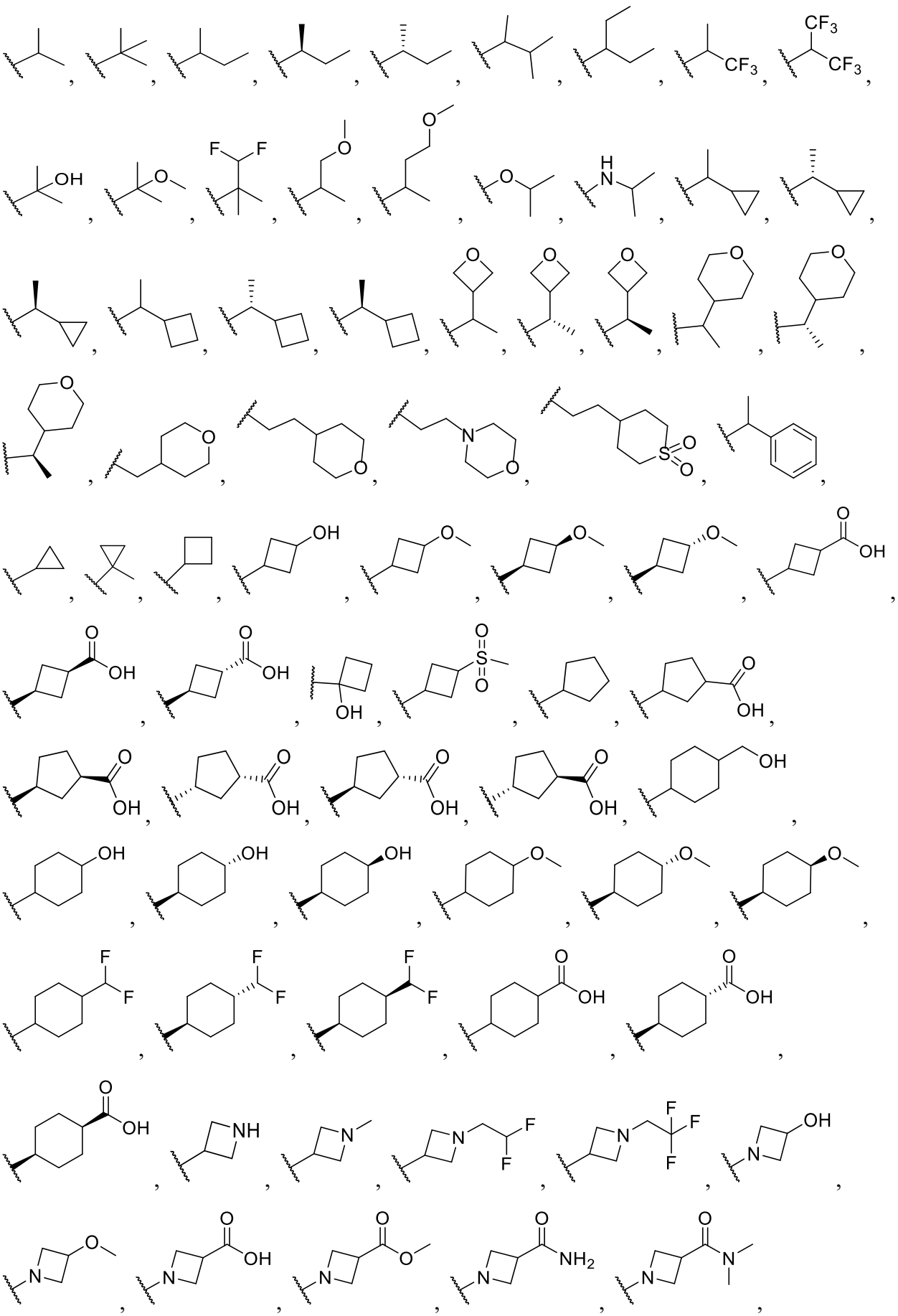
preferably, R is selected from the following groups:

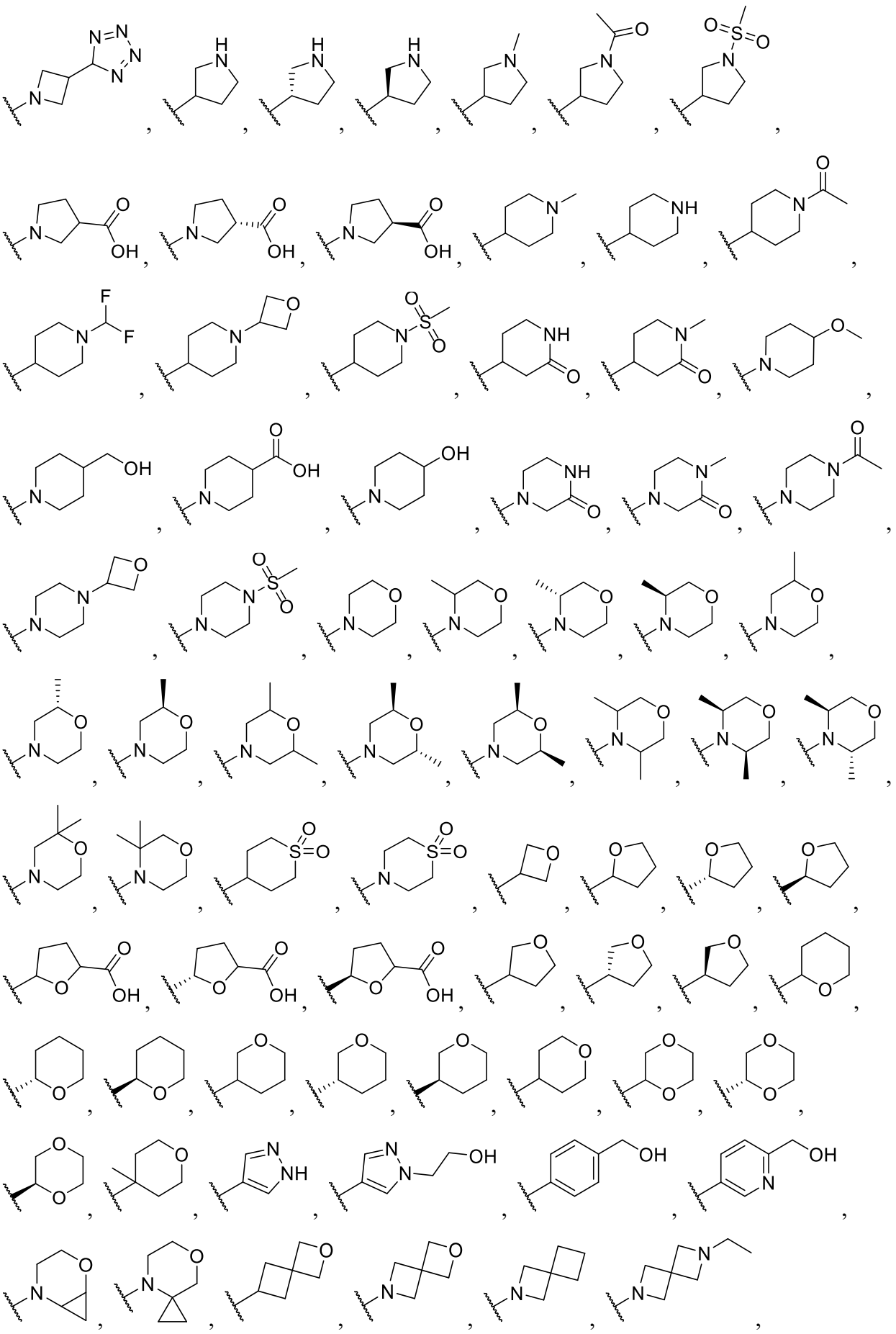


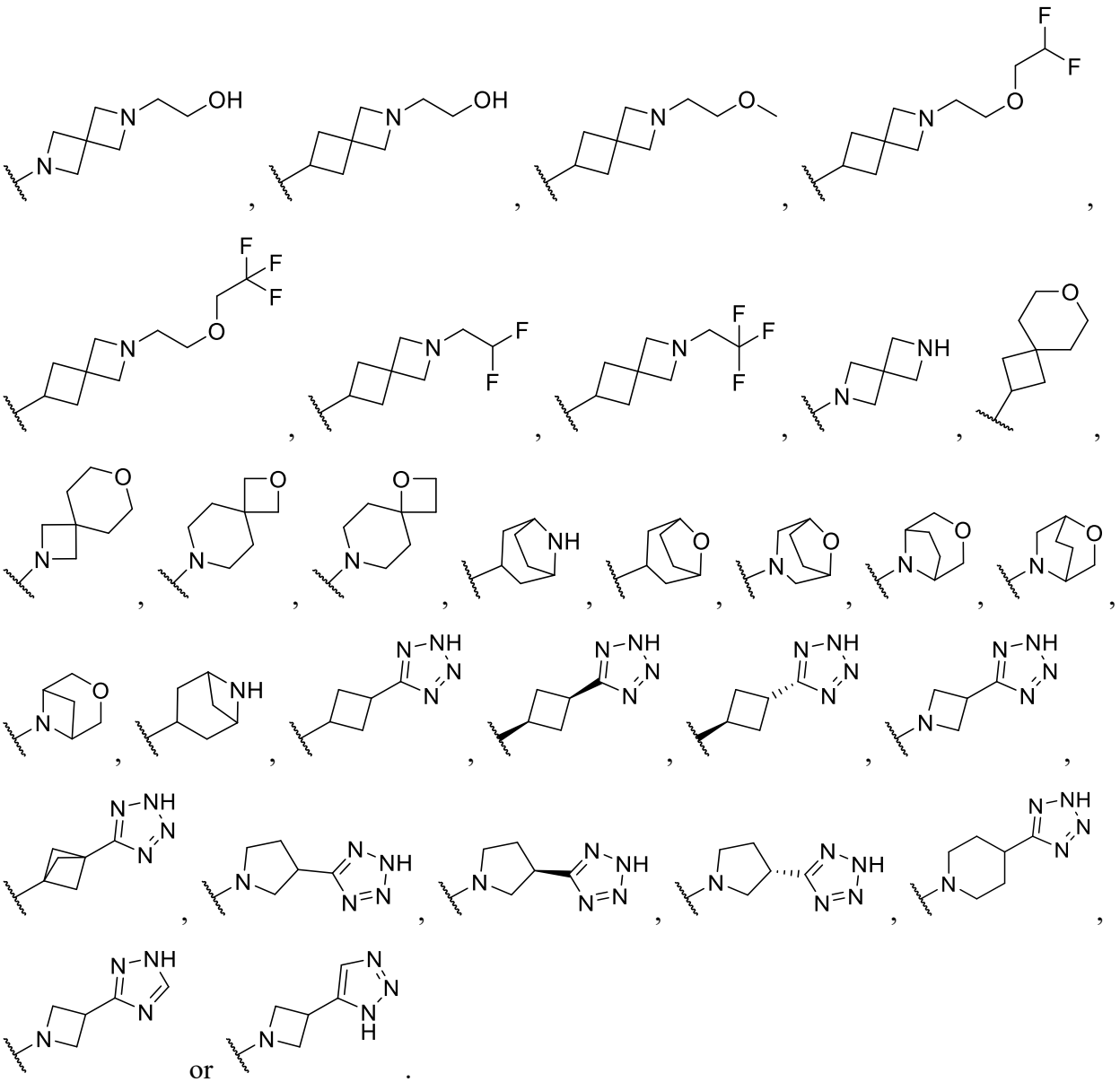




preferably, -L-R is selected from the following groups:

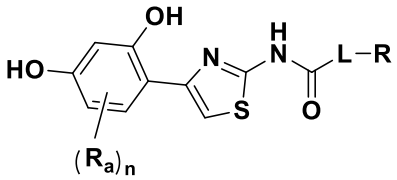






or .

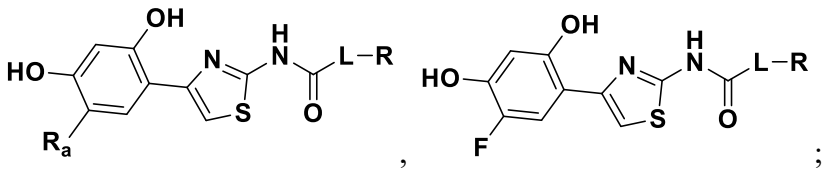
5. The compound according to any one of claims 1 to 4, wherein the compound represented by formula (I) is selected from the following structures:



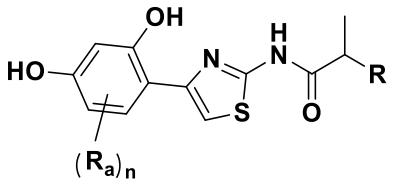
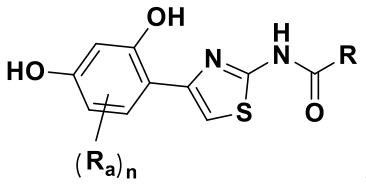
(I-1)

wherein R_a, L, R and n are as defined in any one of claims 1 to 4;

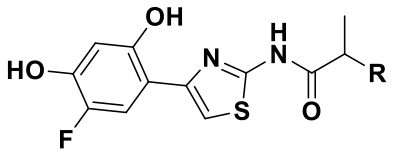
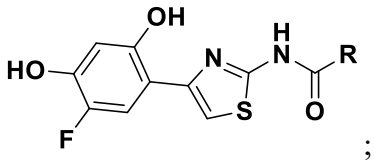
preferably, the compound represented by formula (I) is selected from the following structures:



(IA-1) (IA-2)

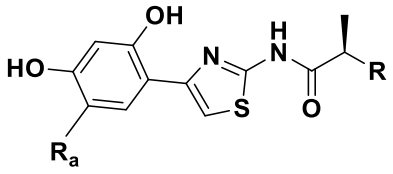
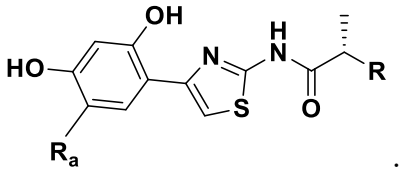
(IA-3) (IA-4)

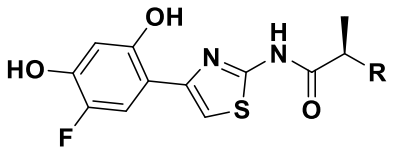
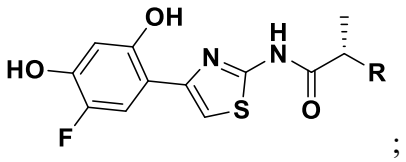
(IA-5) (IA-6)

wherein R_a, L, R and n are as defined in any one of claims 1 to 4;

preferably, the compound represented by formula (I) is selected from the following structures:

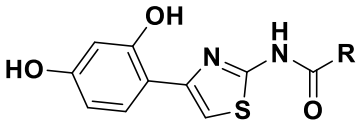
(IB-1) (IB-2)

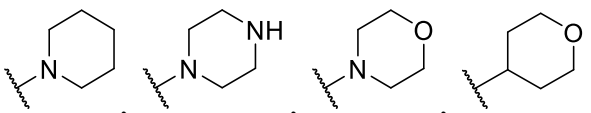
(IB-3) (IB-4)

wherein R_a and R are as defined in any one of claims 1 to 4;

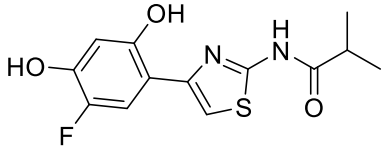
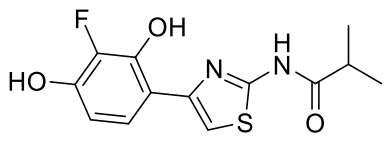
preferably, the compound represented by formula (I) is selected from the following structures:



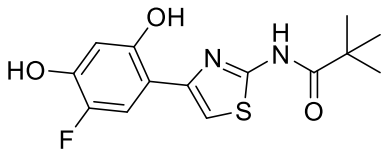
(I-2)

wherein R is as defined in any one of claims 1 to 4, provided that R cannot be the following groups: unsubstituted C_{3-8} cycloalkyl, .

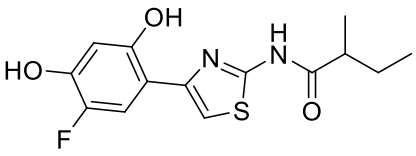
6. The compound according to any one of claims 1 to 5, wherein the compound has the following structures:

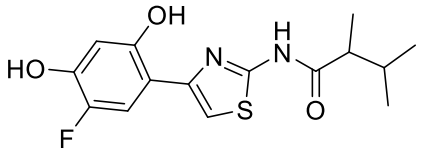
Cpd-01 , Cpd-02 ,



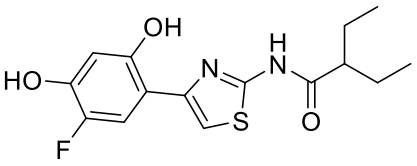
Cpd-03 ,



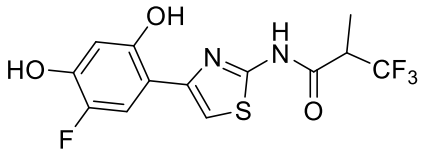
Cpd-04 ,



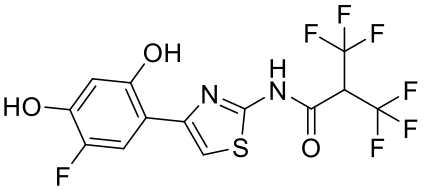
Cpd-05 ,



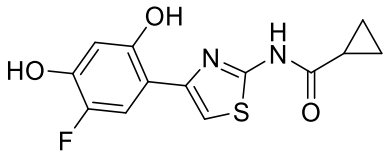
Cpd-06 ,



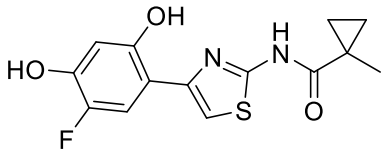
Cpd-07 ,



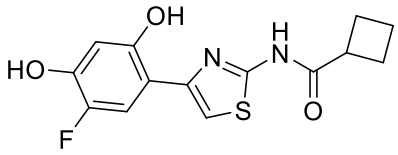
Cpd-08 ,



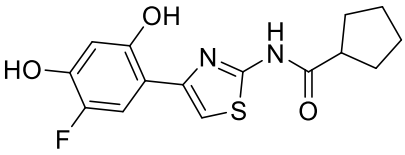
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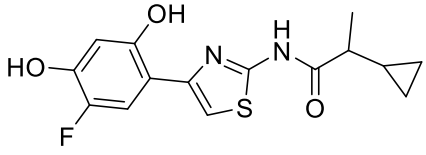
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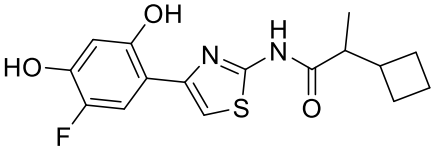
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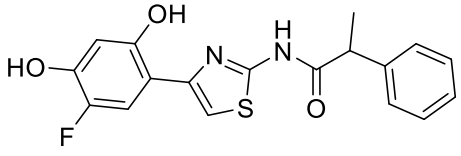
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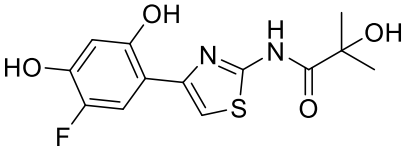
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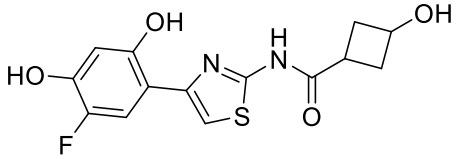
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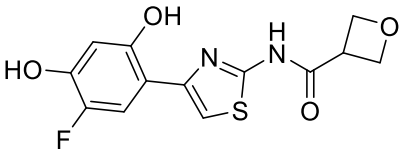
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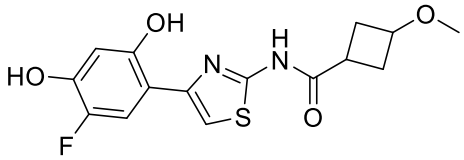
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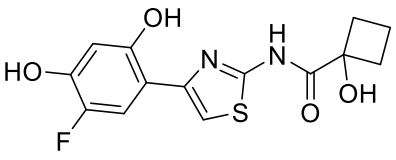
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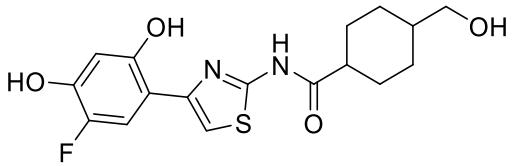
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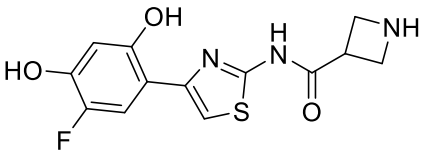
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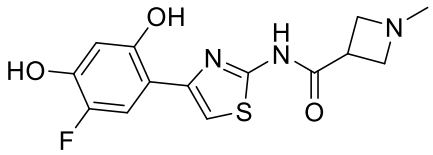
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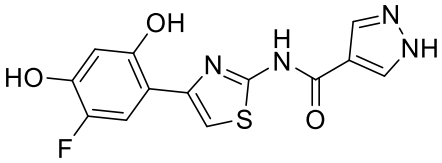
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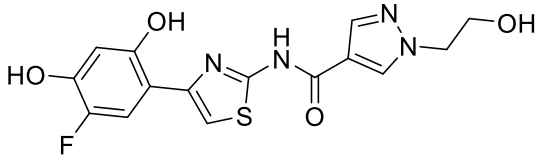
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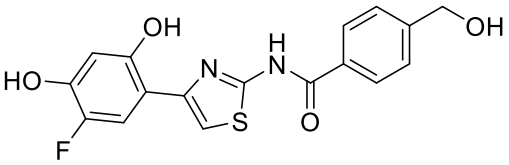
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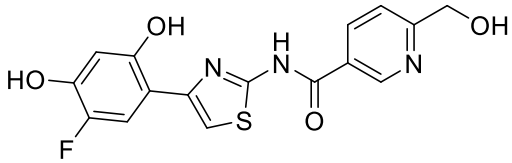
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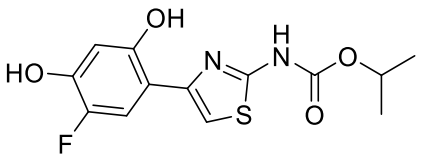
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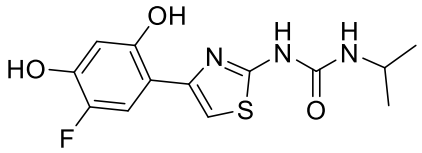
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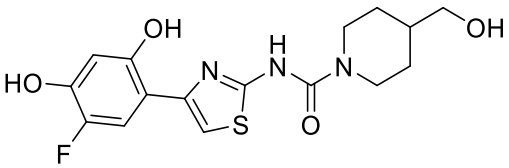
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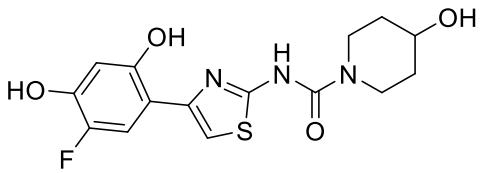
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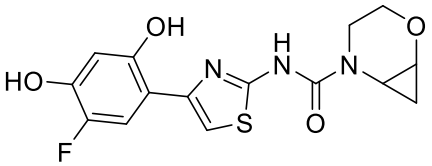
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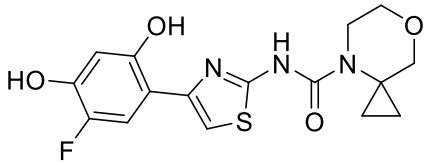
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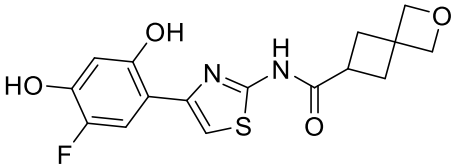
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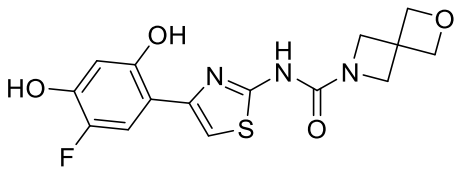
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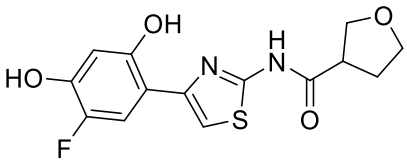


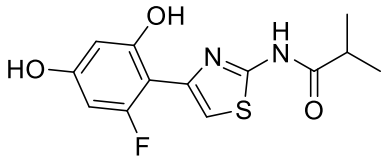
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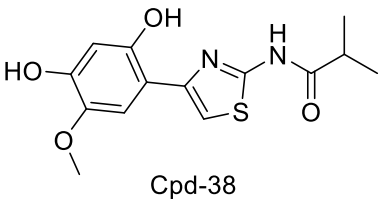


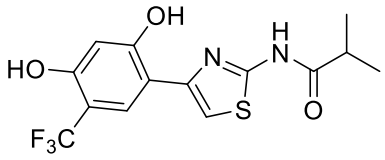
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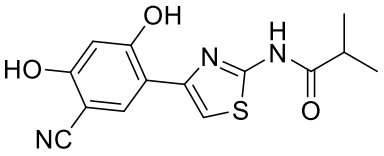


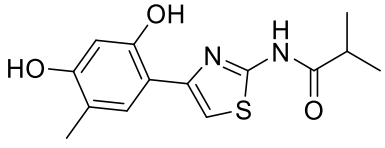
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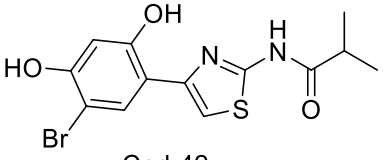


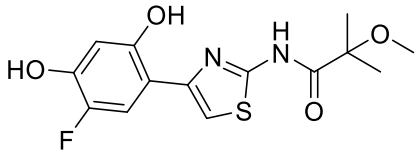
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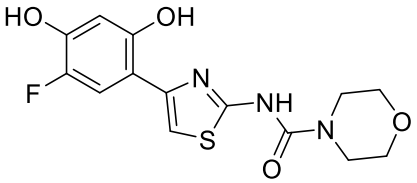


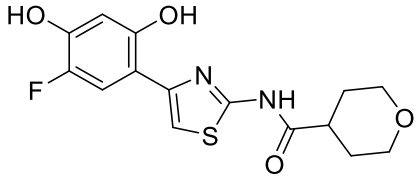
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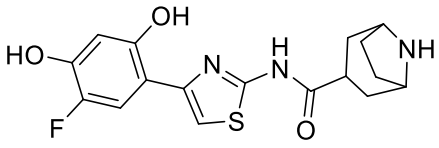


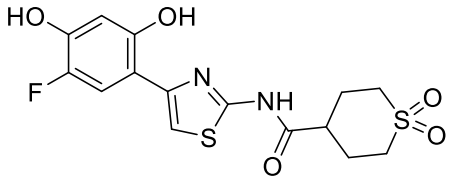
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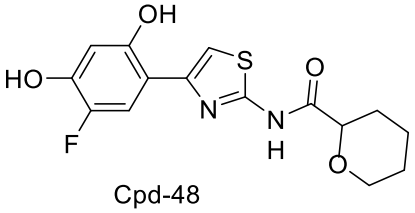


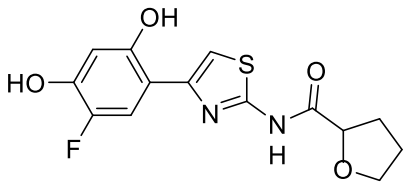
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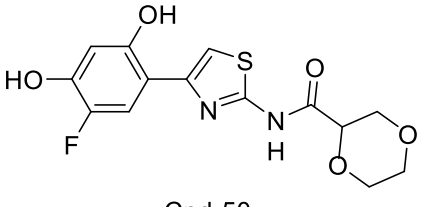


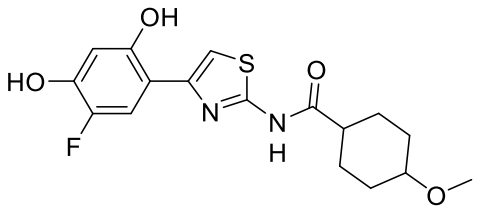
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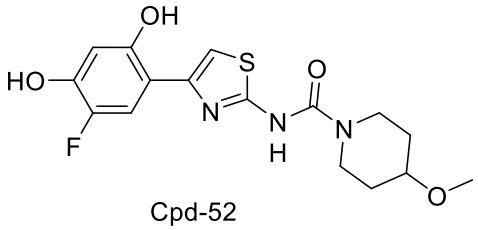
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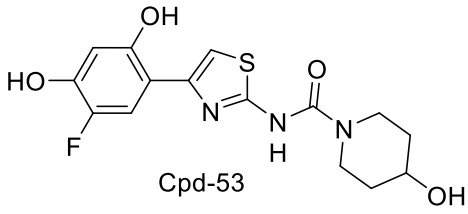
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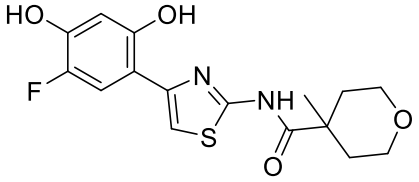
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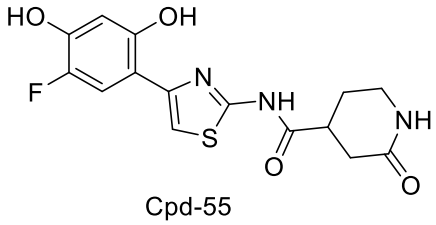
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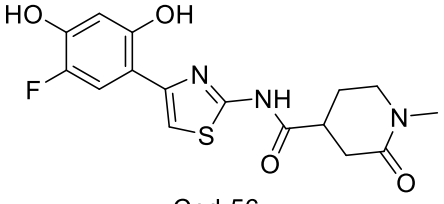
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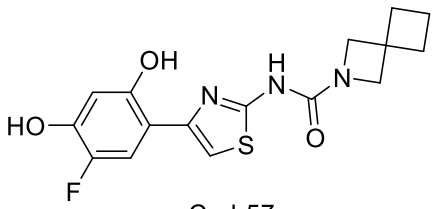
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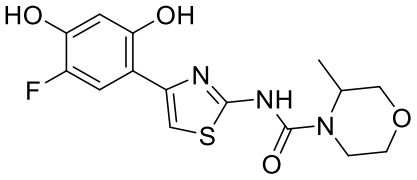
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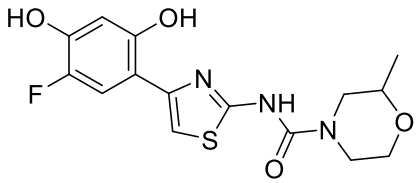
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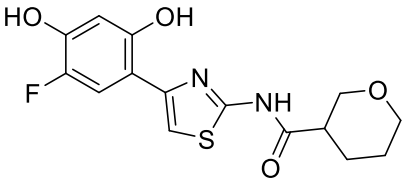
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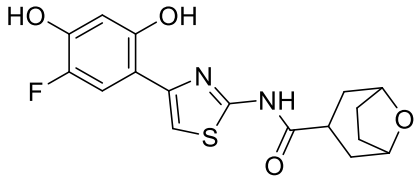
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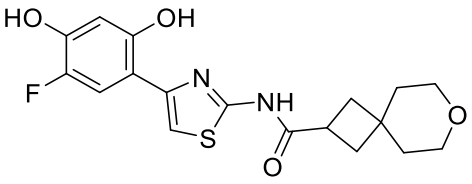
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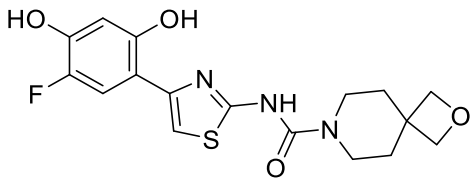
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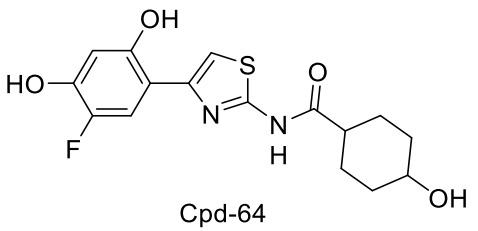
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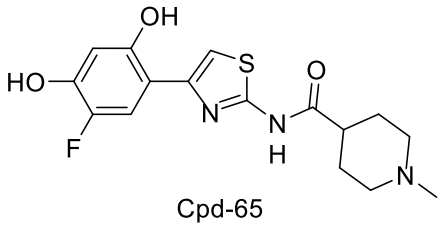
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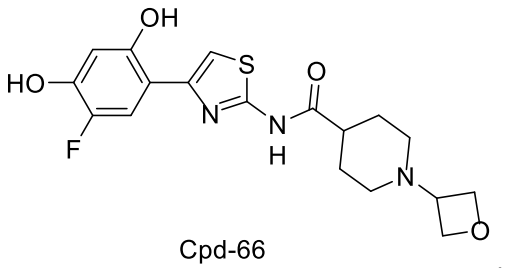
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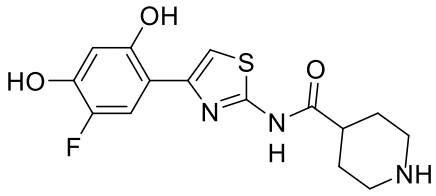
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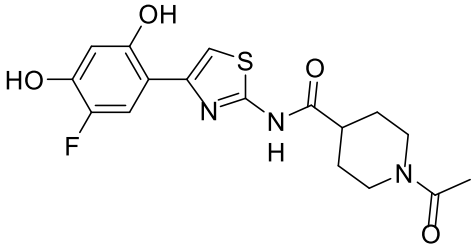
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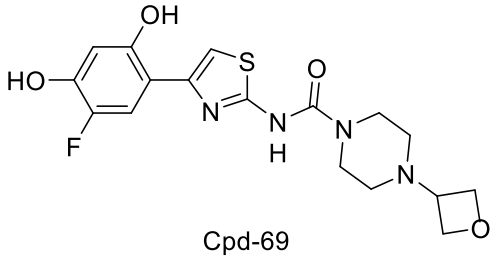
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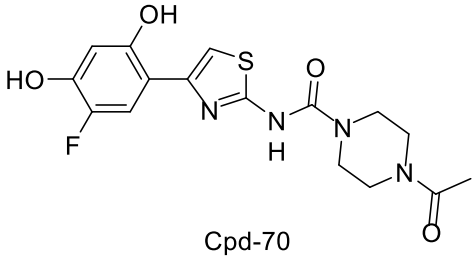
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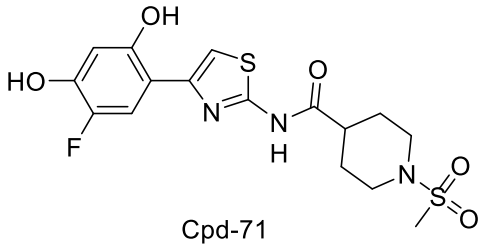
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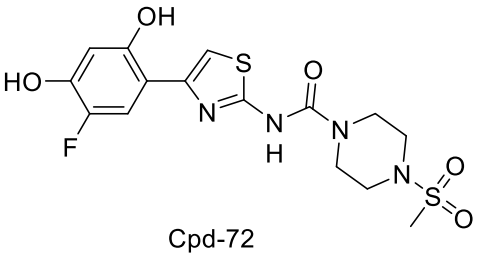
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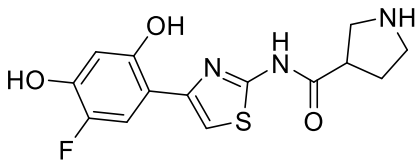
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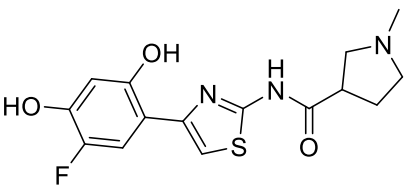
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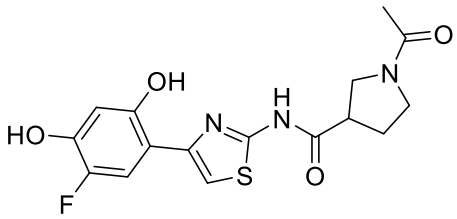
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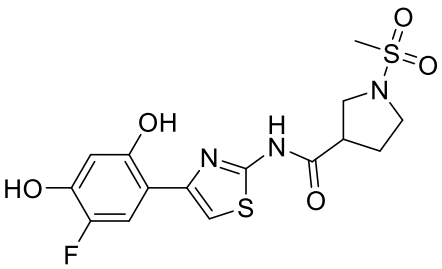
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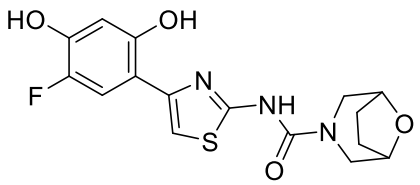
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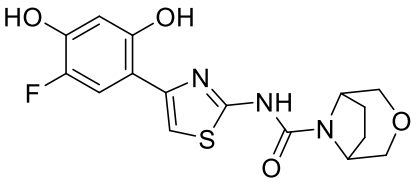
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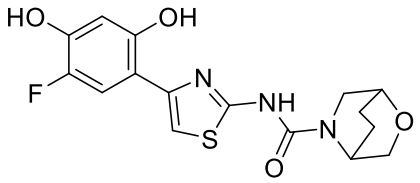
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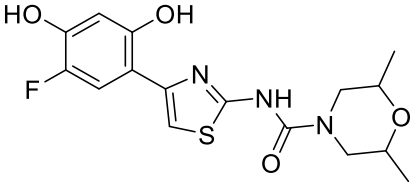
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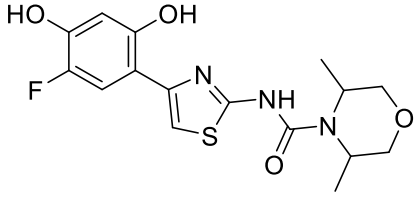
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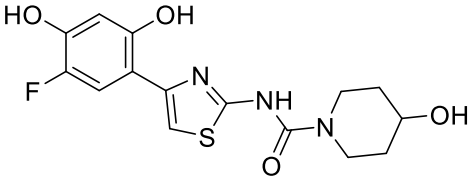
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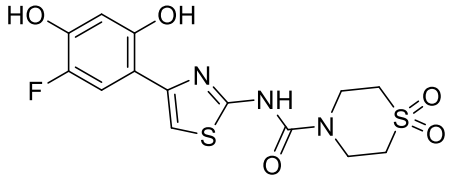
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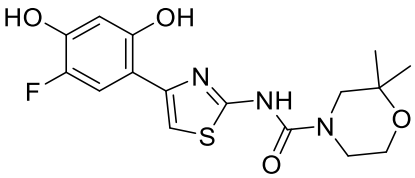
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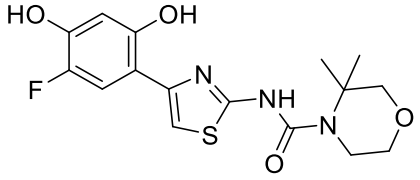
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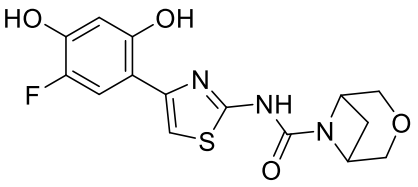
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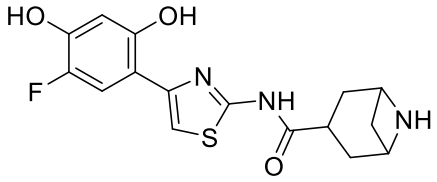
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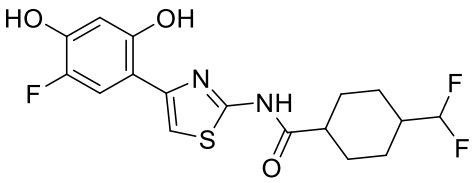
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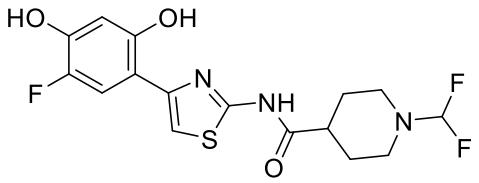
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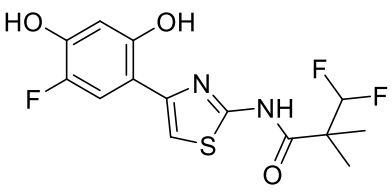
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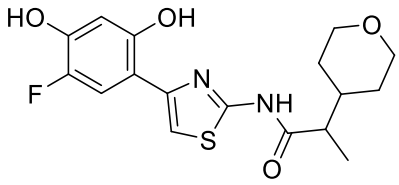
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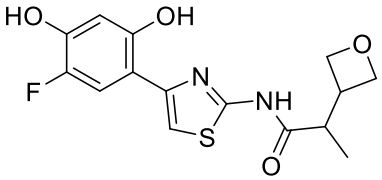
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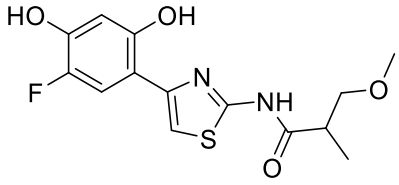
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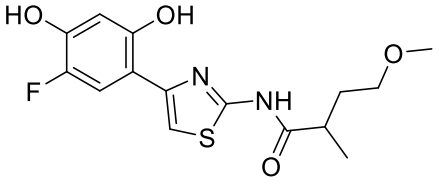
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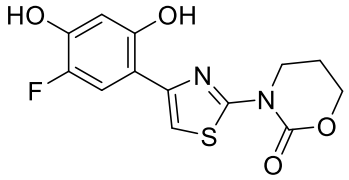
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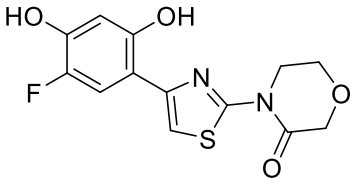
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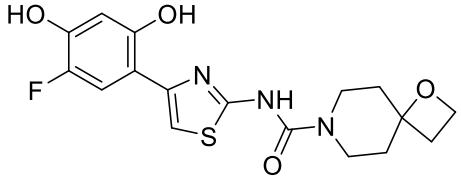
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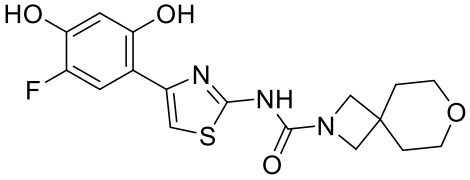
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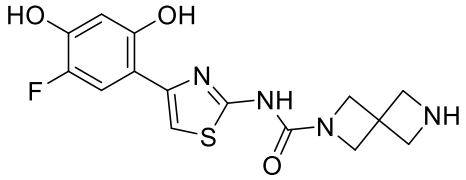
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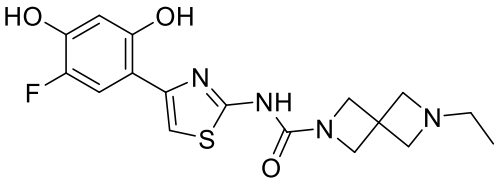
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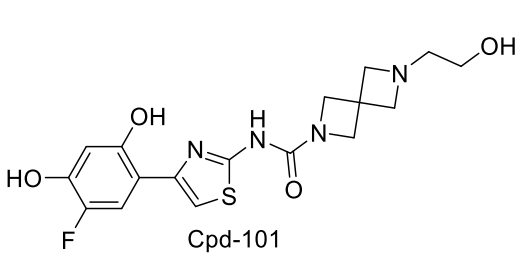
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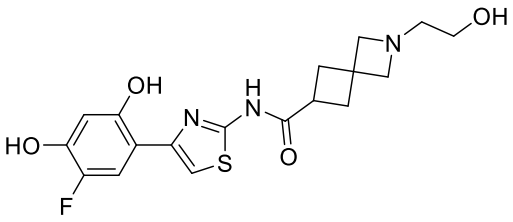
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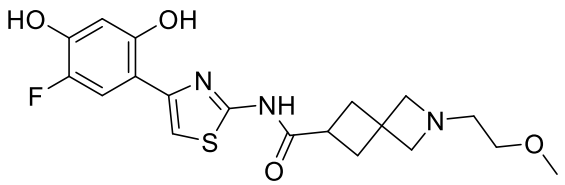
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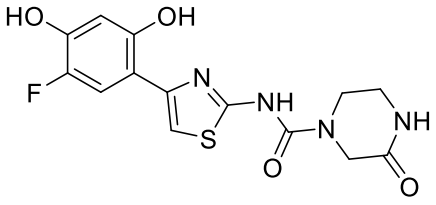
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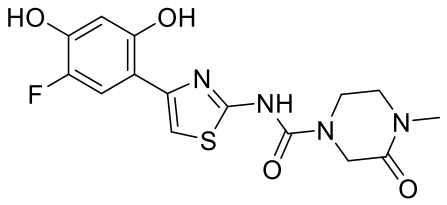
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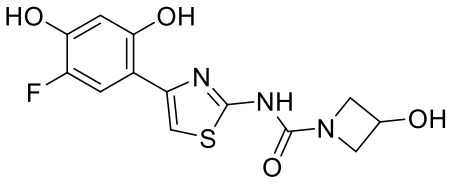
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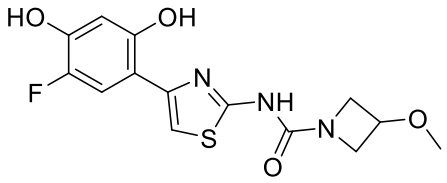
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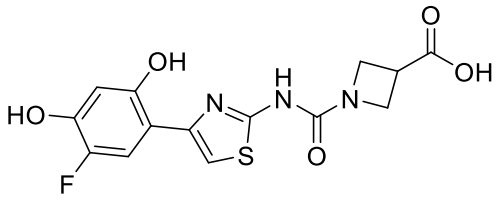
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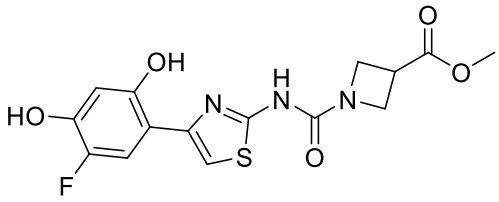
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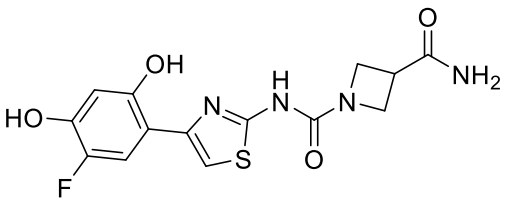
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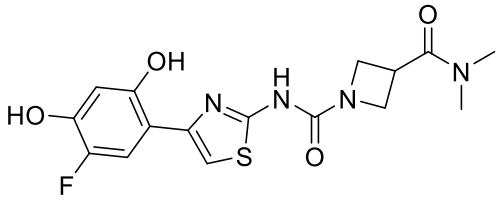
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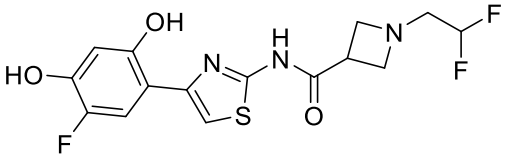
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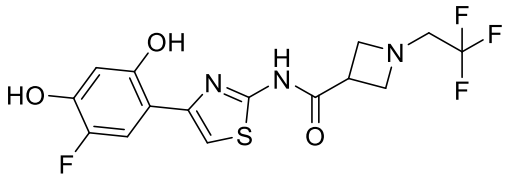
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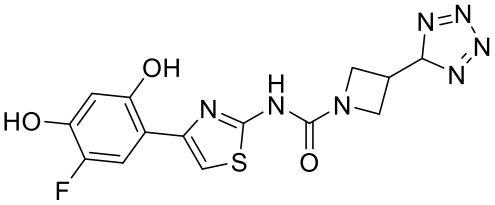
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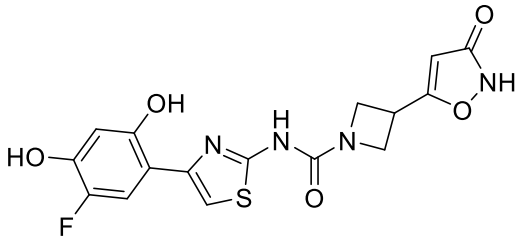
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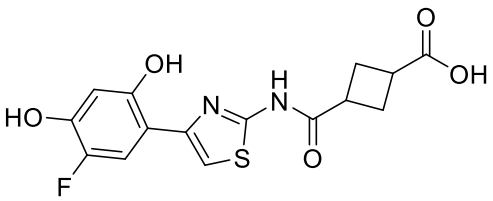
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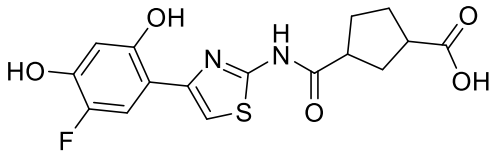
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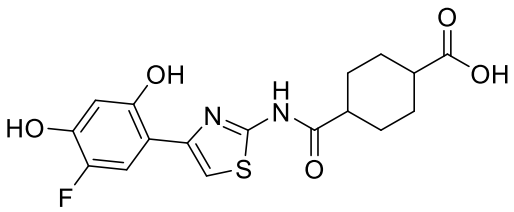
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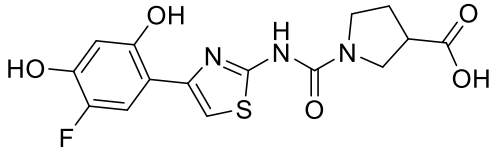
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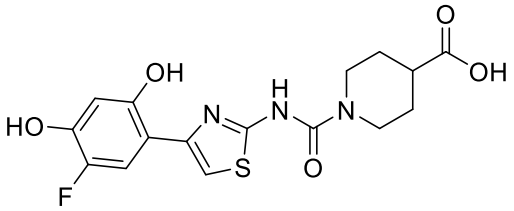
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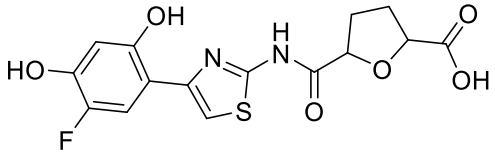
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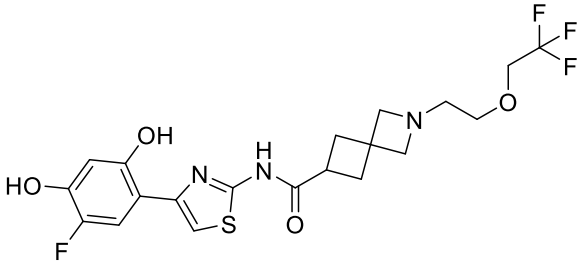
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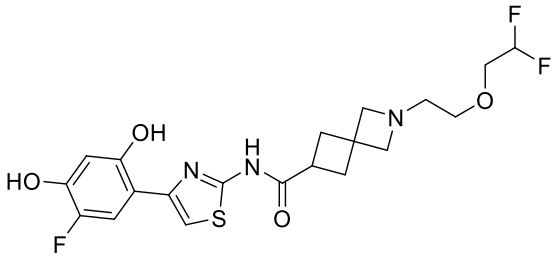
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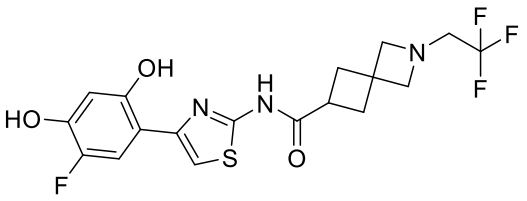
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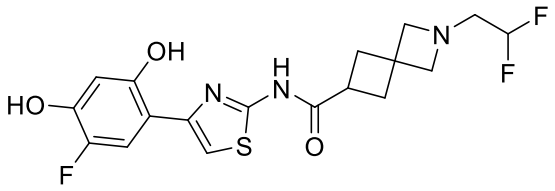
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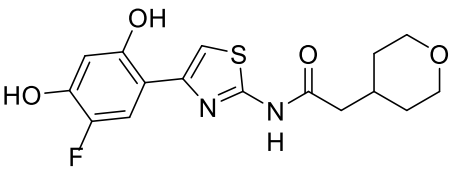
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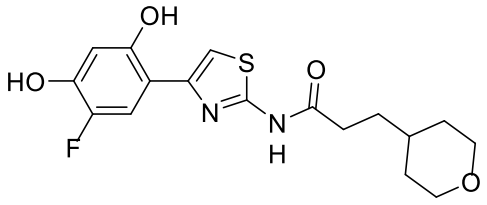
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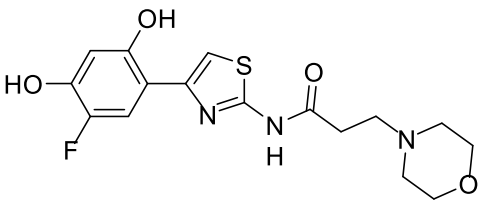
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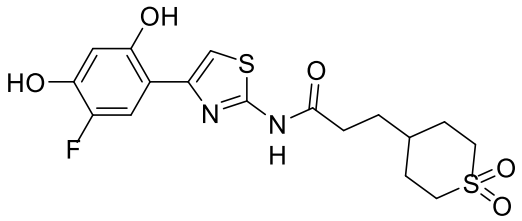
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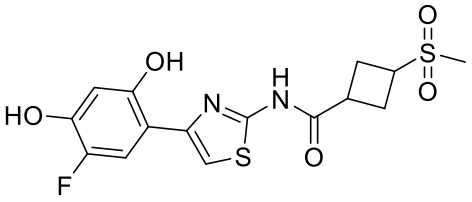
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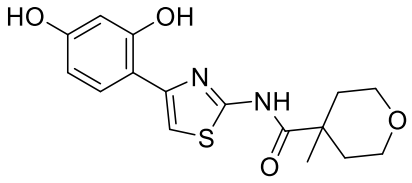
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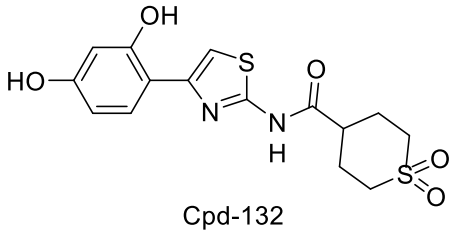
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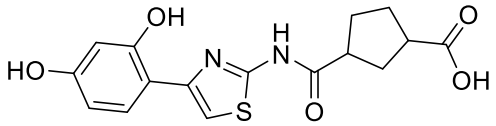
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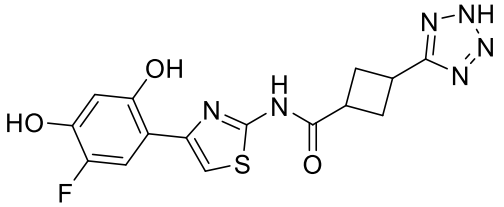
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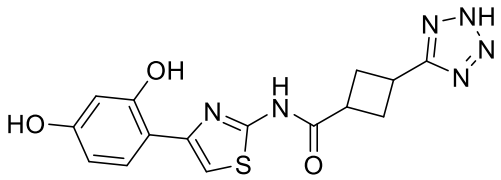
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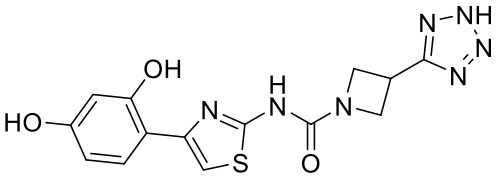
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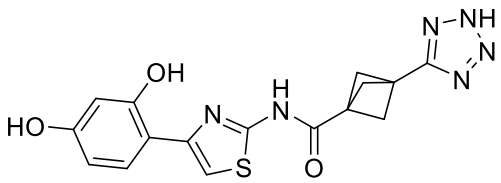
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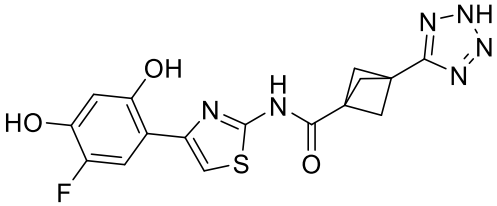
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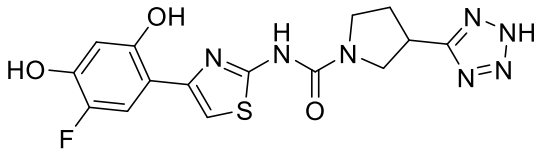
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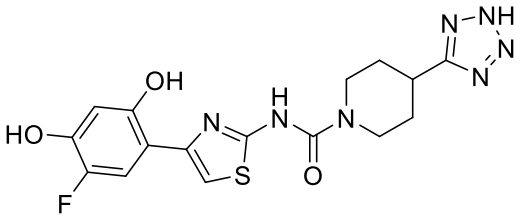
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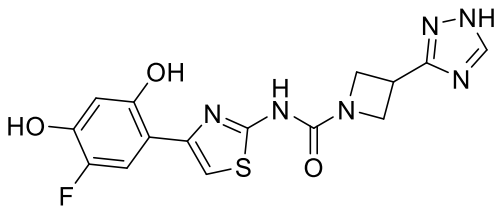
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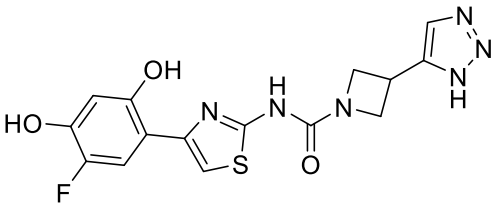
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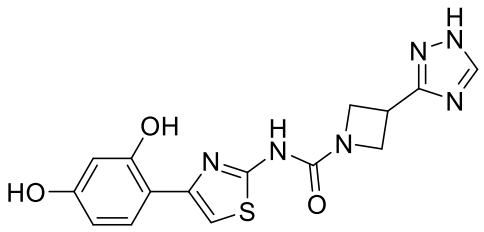
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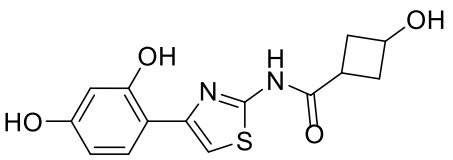


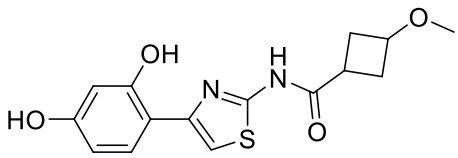
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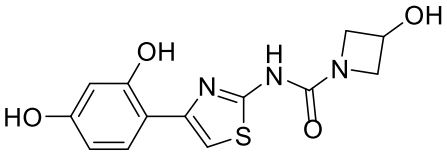


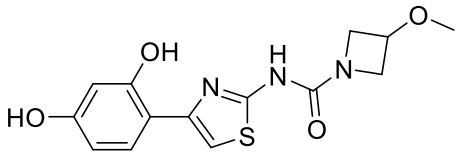
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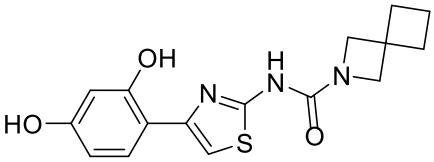


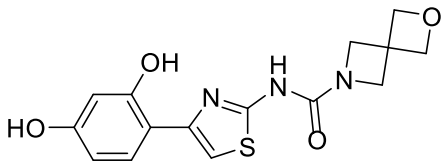
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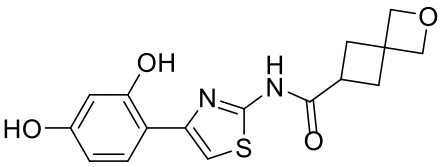
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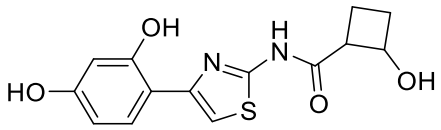
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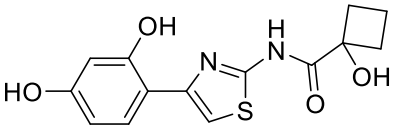
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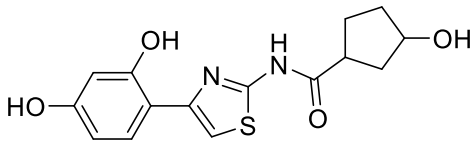
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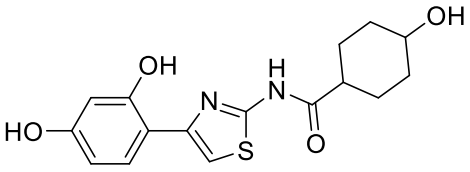
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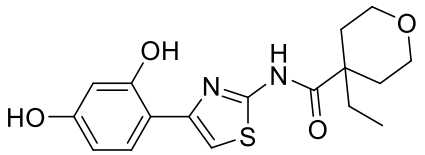
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Cpd-150 , 

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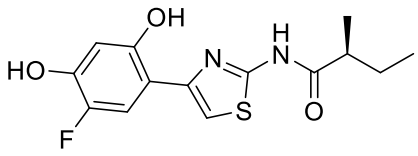
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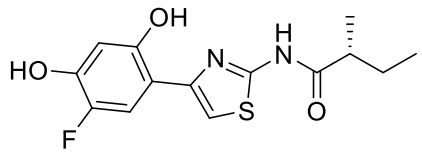
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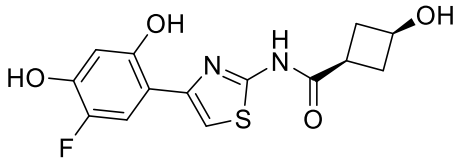
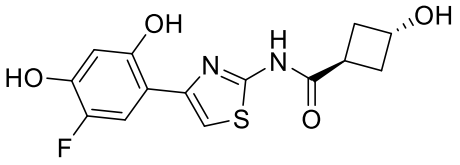
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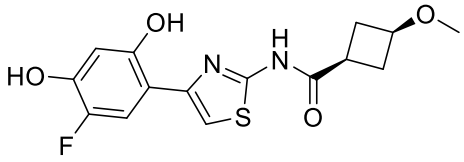
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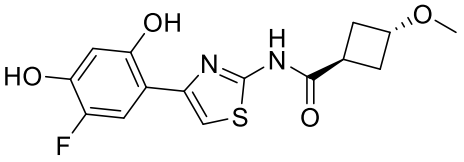


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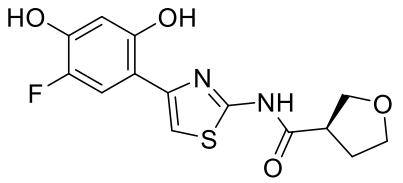
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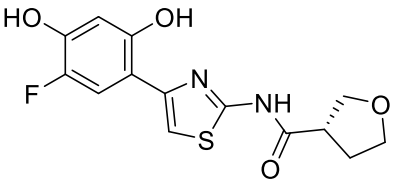
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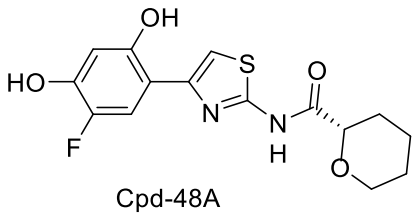
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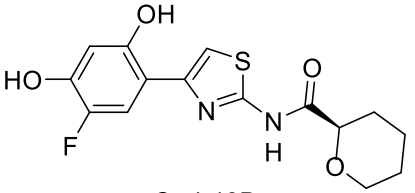
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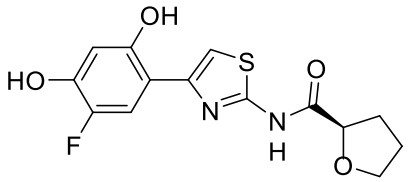
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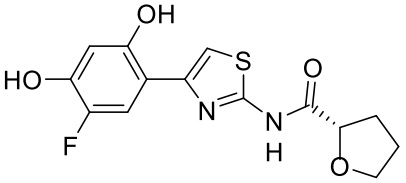
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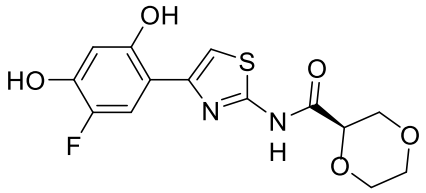
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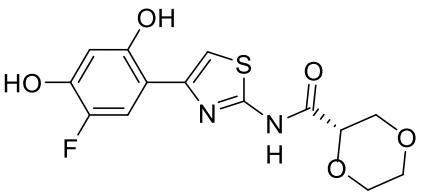
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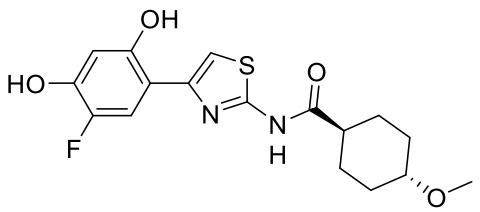
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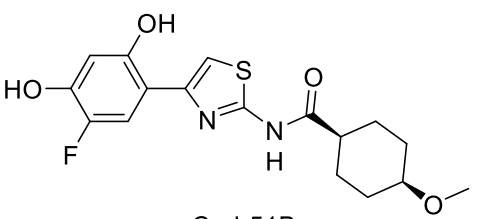
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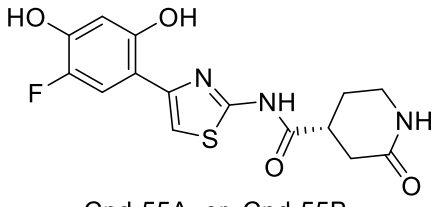
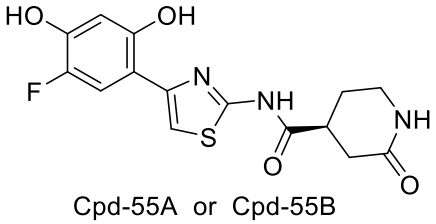
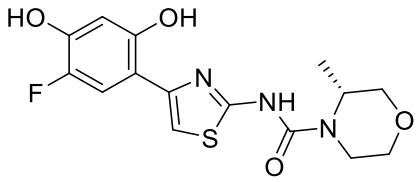
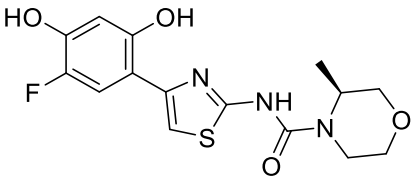
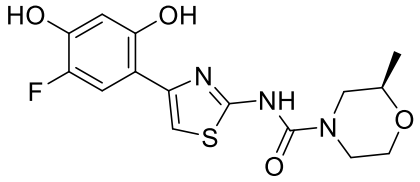
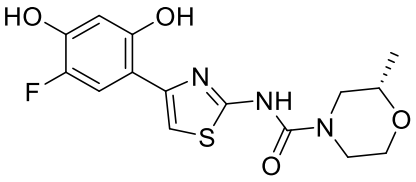
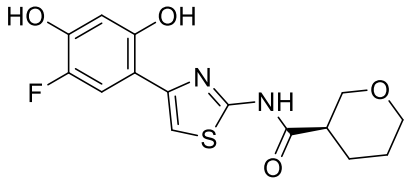
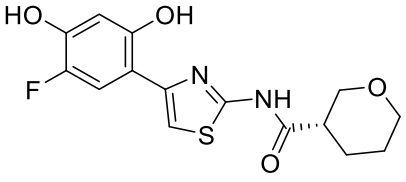
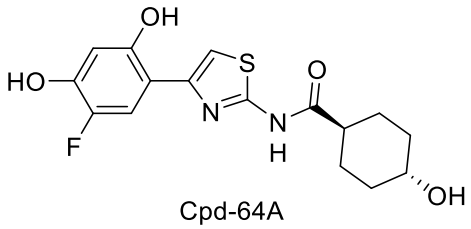
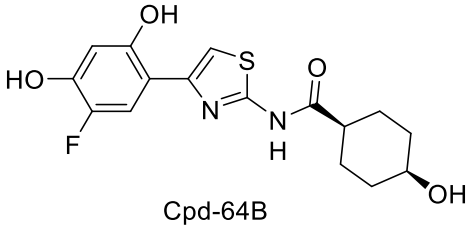
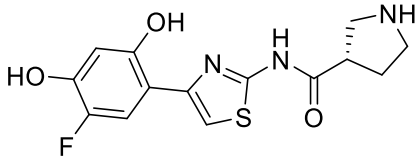
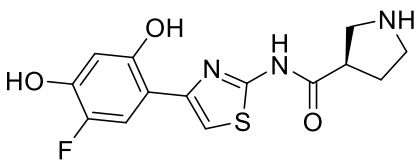
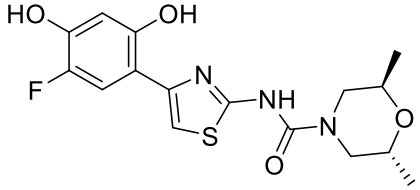
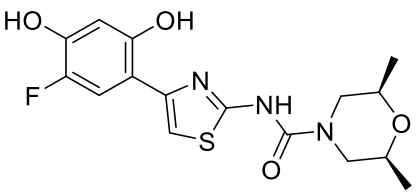
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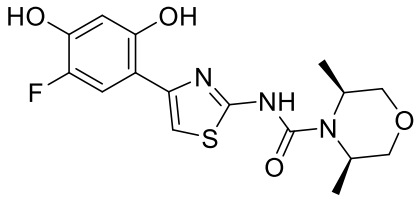
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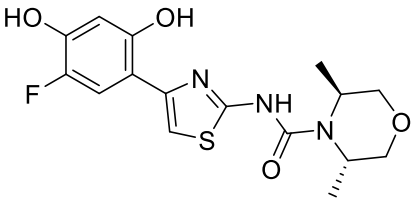


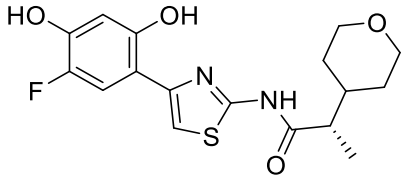
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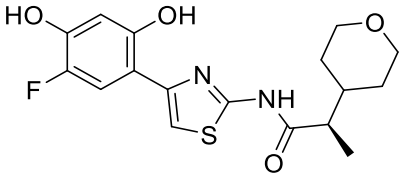
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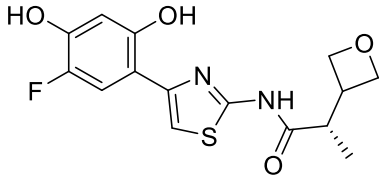

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Cpd-55A or Cpd-55B ,

Cpd-58A ,

Cpd-58B ,

Cpd-59A ,

Cpd-59B ,

Cpd-60A ,

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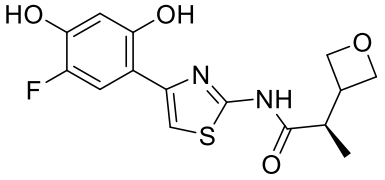


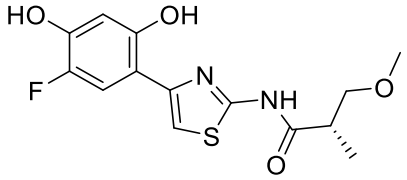
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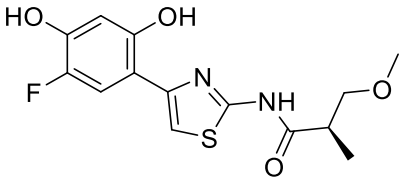


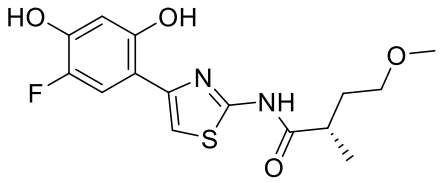
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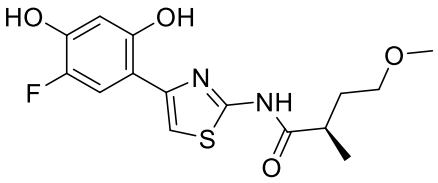


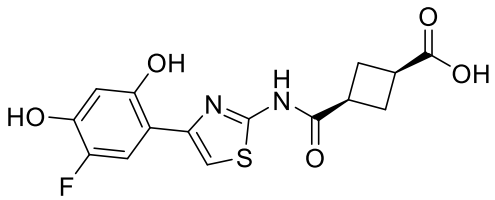
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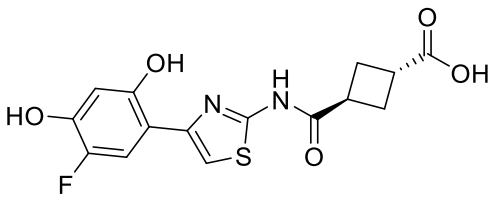


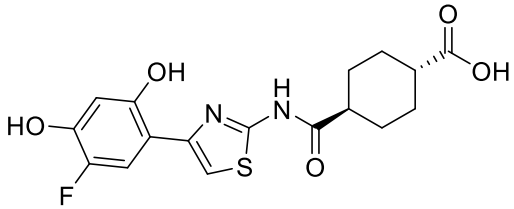
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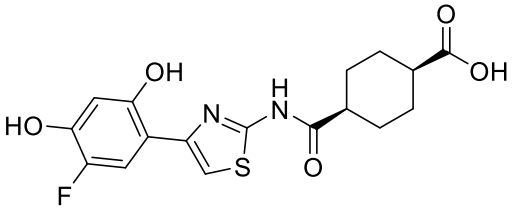


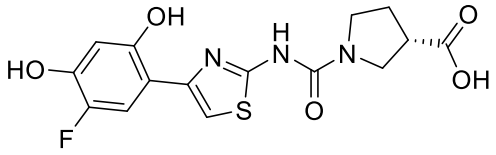
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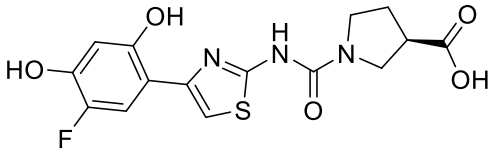


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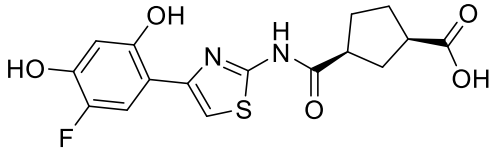
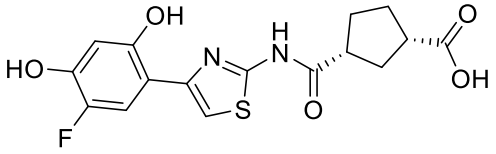


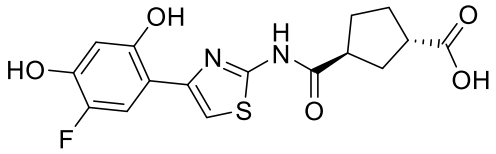
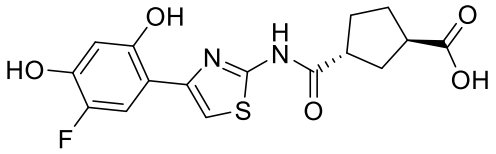
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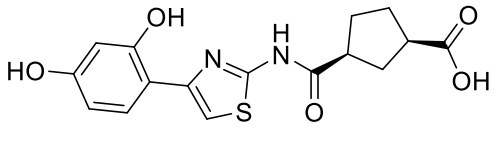
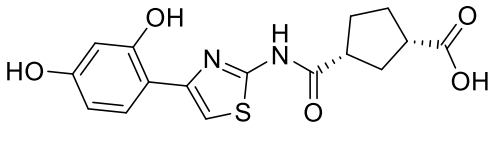


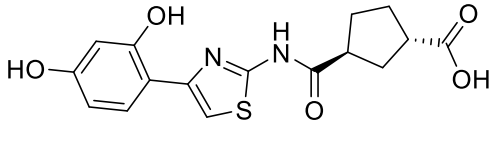
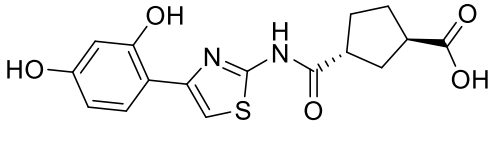
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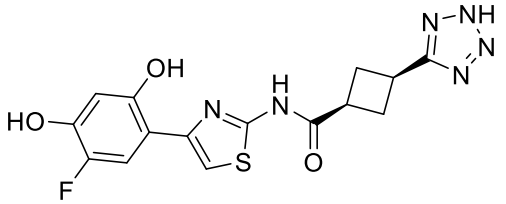
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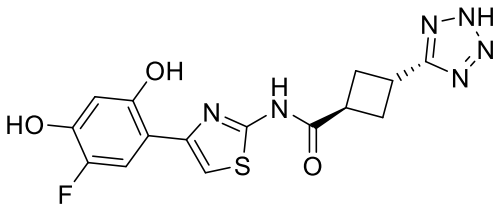
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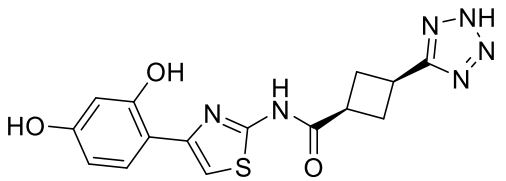
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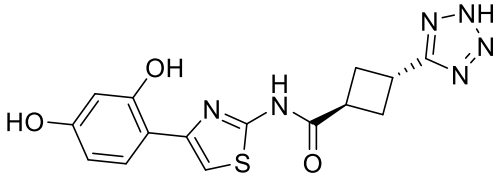
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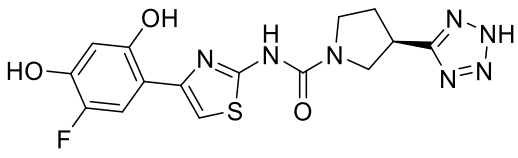
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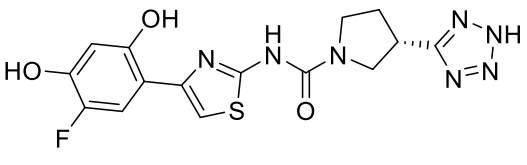
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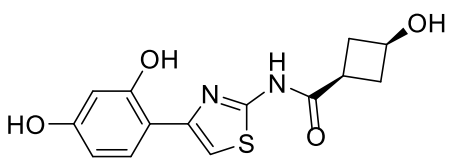
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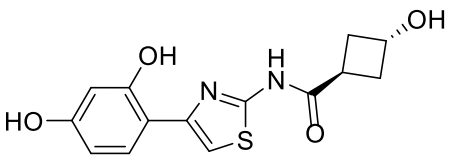
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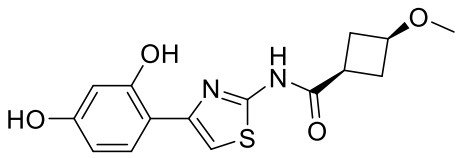
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Cpd-139A or Cpd-139B ,

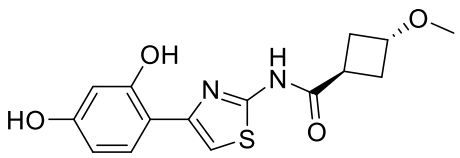


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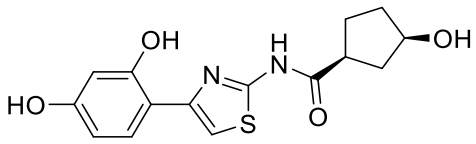
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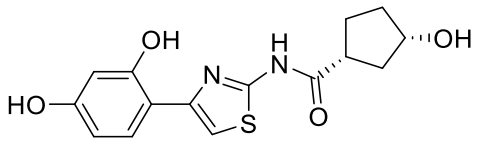
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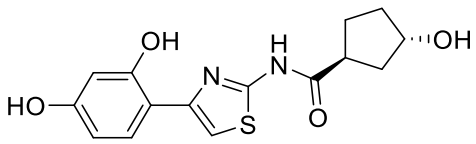
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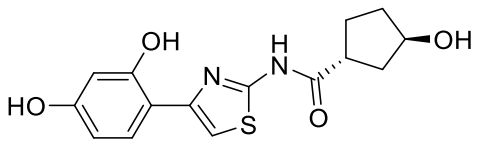
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7. A pharmaceutical composition, comprising a therapeutically effective amount of at least one of the compound, racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof according to any one of claims 1 to 6;

preferably, the pharmaceutical composition further comprises one or more pharmaceutically acceptable excipients.

8. A method for treating tyrosinase-mediated diseases, comprising administering to a patient a prophylactically or therapeutically effective amount of at least one of the compound, racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof according to any one of claims 1 to 6 or the pharmaceutical composition according to claim 7;

preferably, the tyrosinase-mediated disease is tyrosinase-mediated skin pigmentation;

preferably, the symptoms of skin pigmentation are selected from chloasma, striae gravidarum, solar lentigines, café-au-lait spots, or freckles;

preferably, the tyrosinase-mediated skin pigmentation includes post-inflammatory pigmentation, wherein the inflammation is selected from acne, eczema, dermatitis, drug eruption, infection, sunburn, or trauma.

9. Use of at least one of the compound, racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or prodrug compounds thereof according to any one of claims 1 to 6 or the pharmaceutical composition according to claim 7 in the preparation of a drug;

preferably, the tyrosinase-mediated disease is tyrosinase-mediated skin pigmentation;

preferably, the symptoms of skin pigmentation are selected from chloasma, striae gravidarum, solar lentigines, café-au-lait spots, or freckles;

preferably, the tyrosinase-mediated skin pigmentation includes post-inflammatory pigmentation, wherein the inflammation is selected from acne, eczema, dermatitis, drug eruption, infection, sunburn, or trauma.

10. A cosmetic composition comprising an effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, pharmaceutically acceptable salts thereof or derivatives thereof;

preferably, the cosmetic composition further comprises one or more auxiliaries and/or additives, including thickeners, fillers, fragrances, colorants, emulsifiers, additional active ingredients such as vitamins or proteins, photoprotective agents, stabilizers, insect repellents, alcohols, water, salts, antibacterial agents, proteolytic or keratolytic active substances, and the like.

11. A non-therapeutic cosmetic method, comprising administering to a mammal in need thereof an effective amount of at least one of a compound represented by formula (I), racemates, stereoisomers, tautomers, solvates, polymorphs, acceptable salts thereof or derivatives thereof, or the cosmetic composition according to claim 10, for ameliorating/adjuvantly treating the symptoms of tyrosinase-mediated skin pigmentation, or for skin whitening;

preferably, the method comprises administering an effective amount of the cosmetic composition to a mammal in need thereof, for ameliorating/adjuvantly treating the symptoms of tyrosinase-mediated skin pigmentation, or for skin whitening;

preferably, the symptoms of tyrosinase-mediated skin pigmentation are selected from chloasma, striae gravidarum, solar lentigines, café-au-lait spots, or freckles;

preferably, the tyrosinase-mediated skin pigmentation includes post-inflammatory pigmentation, wherein the inflammation is selected from acne, eczema, dermatitis, drug eruption, infection, sunburn, or trauma.